Draft Comparative Effectiveness Review

Number XX (Provided by AHRQ)

Comparative Effectiveness of Treatments for Low Bone Density (Including Osteoporosis)

Prepared for:
Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

This draft report has been revised to correct an erroneous conclusion that Raloxifene is associated with an increased risk of serious cardiac events. The conclusion was caused by a computing error. Appropriate changes have been made to the relevant text on pages 3, 68, 72 and 74 and to the tables on page 67 of Appendix C1 and page 2 of Appendix F.

Prepared by:
Southern California/RAND Evidence-based Practice Center
Santa Monica, CA

Prinicipal Investigator
Catherine MacLean, MD, PhD

Research Team
Alicia Alexander, MD
Jason Carter, BA
Susan Chen, BA
Jennifer Grossman, MD
Margaret Maglione, MPP
Maureen McMahon, MD
Melissa McNamara, MD
Walter Mojica, MD
Veena Ranganath, MD
Marika Suttorp, MS
Martha Timmer, MS

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that systematic comparative effectiveness reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence. Therefore, all comparative effectiveness reviews are accompanied by information tailored to the public.

Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative effectiveness reviews will be updated regularly.

This report is based on research conducted by the Southern California Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXXX). The findings and conclusions in this document are those of the authors who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of the Agency for Healthcare Research and Quality or of the U.S. Department of Health and Human Services.

This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Acknowledgments

* PENDING *

Technical Expert Panel

Marc C. Hochberg, MD, MPH, University of Maryland School of Medicine, Baltimore, MD

Lee J. Melton III, MD, MPH, Mayo Clinic, Rochester, MN

Paul D. Miller, MD, FACP, Colorado Center for Bone Research, Lakewood, CO

Marcel E. Salive, MD, MPH, Center of Medicare and Medicaid Services, Baltimore, MD

Katherine Sherif, MD, Drexel University College of Medicine, Philadelphia, PA

Contents

Tables

Figures

Appendices

Appendices and Evidence Tables are provided electronically at ***http://www.ahrq.gov/clinic/epcindex.htm***

Comparative Effectiveness of Treatments for Low Bone Density (Including Osteoporosis)

Executive Summary

Prepared for the Effective Health Care Program

Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services

The Effective Health Care program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions for treating difficult health problems. The object is to help consumers, health care providers and others in making informed choices among treatment alternatives. Through its comparative effectiveness reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high priority health conditions. It also promotes and generates new scientific evidence, by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at ***www.effectivehealthcare.ahrq.gov*** .

Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] It is especially common in post-menopausal women due to falling estrogen levels. Approximately 25 million people in the United States are affected by osteoporosis or low bone density.[2] The clinical complications of osteoporosis include fractures, disability, and chronic pain. It is estimated that 54% of women age 50 and over will sustain an osteoporosis fracture during their lifetime.[3] Approximately 4% of patients over age 50 who experience a hip fracture will die while in the hospital, and 24% will die within with year after experiencing the hip fracture.[4] Although the incidence of hip fracture is lower among men than women, the one-year mortality following hip fractures is 1.5 to 2 times higher in men than in women.[5, 6] In the United States in 1995, osteoporosis fractures cost an estimated 13.8 billion dollars.[7]

This report summarizes the available evidence comparing the efficacy and safety of agents used to prevent or treat low bone density, including osteoporosis. Questions addressed in this report are:

Key Question 1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone-density:

- Bisphosphonate medications, specifically: alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid
- Calcitonin
- Calcium
- Estrogen for women
- PTH
- Selective estrogen receptor modulators (SERMs), specifically: raloxifene and tamoxifen
- Testosterone for men
- Vitamin D
- Combinations of above
- Exercise in comparison to above agents

Key Question 2. How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment), age, gender, glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized; vitamin D deficient vs. not)?

Key Question 3. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?

Key Question 4. What are future directions for research in this area?

Conclusions

Key Question 1

- There is good evidence from randomized trials that, compared with placebo, the bisphosphonates alendronate, ibandronate and residronate; calcitonin; and raloxefine prevent vertebral fractures.
- There is evidence from one randomized controlled trial (RCT) that compared with placebo, 1-34 PTH prevents vertebral fractures.
- There is good evidence from RCTs that compared with placebo, risedronate prevents hip fractures.
- There is good evidence from one large RCT that compared with placebo, estrogen prevents hip fractures.
- Based on limited data, superiority for the prevention of fractures has not been demonstrated for any agent within the bisphosphonate class.

- Based on limited data, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison to calcitonin, calcium, raloxefine or vitamin D.
- Based on a large body of evidence, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison to estrogen.
- There are no data from RCTs on the effect of testosterone on the prevention of fractures.
- There are no data from RCTs on the effect of exercise relative to agents used to treat or prevent osteoporosis on fracture prevention.

Key Question 2

- In the majority of studies identified for this report, the population was post-menopausal women with osteopenia or osteoporosis.
- There is good evidence from RCTs that, compared with placebo, the bisphosphonates alendronate, ibandronate and risedronate; calcitonin; 1-34 PTH; and raloxefine prevent vertebral fractures among post-menopausal women.
- There is evidence from one RCT that, compared with placebo, 1-34 PTH prevents non-vertebral fractures among post-menopausal women.
- There is good evidence from RCTs that, compared with placebo, risedronate prevents hip fractures among post-menopausal women.
- There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on fractures among transplant recipients and patients chronically treated with corticosteroids.
- There are essentially no data on the effect of agents for the prevention and treatment of osteoporosis on fractures among men.

Key Question 3

- There is good evidence from RCTs that compared with placebo, raloxifene is associated with an increased risk of thromboembolic events (OR 2.11, 95% CI 1.51 to 3.01).
- Over a large body of evidence, no significant association was demonstrated between bisphosphonates and mild upper gastro-esophageal events including reflux and esophagitis.
- There is evidence that etidronate is associated with a significant risk of serious upper GI events relative to placebo (OR for non-esophageal perforations, ulcers, and bleeds =1.32, 95% CI 1.04 to 1.67; OR for serious esophageal events = 1.33, 95% CI 1.05 to 1.68).
- Over a large body of evidence, no significant association has been demonstrated between bisphosphonates other than etidronate and serious upper gastrointestinal events.
- There are no data from osteoporosis RCTs that describe an association between bisphosphonates or any other agents and the development of osteonecrosis.

Remaining Issues

Among therapies directed to prevent or treat osteoporosis, we found no studies that assessed the effect of testosterone in men on the development of fractures. Likewise, we did not find any studies with fracture outcomes that compared the effect of drugs with exercise.

Among subpopulations at risk for osteoporosis, there are limited and inconclusive data about the effect of agents to prevent or treat osteoporosis among men, transplant recipients, and people taking corticosteroids regularly. There is little research data on people of color. Future research should address these areas.

A systematic review on bisphosphonates and osteonecrosis of the jaws was published after we submitted our draft report.[8] The article focused on cancer patients. The authors concluded that the risk for osteonecrosis in patients taking bisphosphonates for low bone density is uncertain and warrants future research.

Internet Citation

(to be provided by AHRQ)

Introduction

Background

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] It is especially common in post-menopausal women due to falling estrogen levels. Treatment is aimed at preventing osteoporosis from developing as well as preventing bone loss to reduce the risk of fracture. Approximately 25 million people in the United States are affected by osteoporosis and low bone mass,[2] and it is a major cause of morbidity and mortality in older persons.

The clinical complications of osteoporosis include fractures, disability, and chronic pain. It is estimated that 54% of women age 50 and over will sustain an osteoporosis fracture during their lifetime.[3] Approximately 4% of patients over age 50 who experience a hip fracture will die while in the hospital, and 24% will die within with year after experiencing the hip fracture.[4] Although the incidence of hip fracture is lower among men than women, the one-year mortality following hip fractures is 1.5 to 2 times higher in men than in women.[5, 6] In the United States in 1995, osteoporosis fractures cost an estimated 13.8 billion dollars.[7]

Many guidelines recommended the use of calcium and Vitamin D supplementation for the prevention and treatment of osteoporosis. Exercise is also highly recommended. In addition, various pharmaceutical treatments for low bone density have been approved by the Food and Drug Administration (FDA); they are described below.

Bisphosphonates, are compounds that permanently bind to mineralized bone surfaces and inhibit osteoclasts, thus decreasing bone resorption. Bisphosphonates approved by the FDA include alendronate, etidronate, pamidronate, ibandronate, risedronate, and zolendronic acid. However, not all of these agents are approved for prevention or treatment of osteoporosis. Alendronate, ibandronate and risedronate are approved for the prevention and treatment of postmenopausal osteoporosis. Alendronate is additionally approved for the treatment of osteoporosis in men and to treat glucocorticoid-induced osteoporosis in men and women. Risedronate is additionally approved for the prevention and treatment of glucocorticoid-induced osteoporosis in men and women. Etidronate, pamidronate and zolendronic acid are not approved for the prevention or treatment of osteoporosis, but are used off-label for this purpose. There are several other bisphosphonates, such as toludrinate and clodronate, which have been used in clinical trials of osteoporosis but are not yet approved for the treatment of osteoporosis in the United States. Therefore, they will not be reviewed at this time.

Calcitonin is another agent that has been used in the treatment of osteoporosis. A hormone produced by the follicular cells of the thyroid gland, it has the ability to suppress osteoclast activity, which is one of its proposed mechanisms of efficacy. Calcitonin is available in several forms. Calcitonin is approved by the FDA for the treatment of post-menopausal osteoporosis.

Selective estrogen receptor modulators (SERMs) exhibit a pharmacologic profile characterized by estrogen agonist activity in some tissues with estrogen antagonist activity in other tissues.[9]

The first widely used SERM, tamoxifen, has estrogen antagonist activity in breast tissue and is approved for treatment of breast cancer. Another SERM, raloxifene, exhibits an estrogen agonist profile in the skeletal system. This agent is FDA-approved for the prevention and treatment of post-menopausal osteoporosis.

One of the newest treatments for osteoporosis is human parathyroid hormone (PTH), which helps to regulate calcium metabolism and promotes the growth of new bone. Two analogs of human PTH have been developed for use in the treatment of osteoporosis. Teriparatide (brand name Forteo) is a synthetic form of the first 34 amino acids of human PTH (PTH 1-34). This drug is administered by injection and is FDA-approved for up to 24 months of use for the treatment of osteoporosis among post-menopausal women and hypogonadal men. . Full-length PTH (brand name PReOs) contains all 84 amino acids in human PTH (PTH 1-84). This agent is under review for FDA approval. Because it is not FDA-approved full-length PTH is not reviewed in this report.

Under Section 1013 of the Medicare Modernization Act, the Agency for Healthcare Research and Quality (AHRQ) was instructed to conduct comparative-effectiveness reviews (CER) on medications, devices, and other interventions. The CERs aim to concisely synthesize the evidence, clearly state conclusions about the evidence, and identify research gaps. This CER compares the benefits in fracture reduction and harms from adverse events among and within the various classes of treatment for low bone-density.

Scope and Key Questions

Key Question 1. What are the comparative benefits in fracture reduction (including vertebral and nonvertebral sites [hip, radius, and proximal humerus]) among and also within (particularly for parts a and b) the following treatments for low bone-density:

a. Bisphosphonate medications, specifically: alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid; and between intravenous and orally administered forms

b. Selective estrogen receptor modulators, specifically: raloxifene and tamoxifen

c. Calcitonin

d. PTH

e. Testosterone for men

f. Estrogen for women

g. Calcium

h. Vitamin D in comparison to alternate therapies*

i. Exercise in comparison to alternate therapies

j. Combinations of above

*Will summarize recent meta-analyses on vitamin D, but will not search for, evaluate or summarize individual studies on vitamin D unless vitamin D is a comparator arm to other drugs noted above.

Key Question 2. How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment), age, gender, glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized; vitamin D deficient vs. not)?

Key Question 3. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?

Key Question 4. What are future directions for research in this area?

Table 1 describes characteristics and current indications for the treatments evaluated in this review.

Table 1. Pharmacokinetics, indications and dosing for drugs used to treat or prevent osteoporosis.

Drug	**Trade Names(s)**	**Half-life or other relevant pharmacokinetic feature**	**Labeled indications**	**Dosing**	**Dose adjustments for special populations**
Alendronate	Fosamax	**Absorption** Bioavailability: 0.59% to 0.64% **Distribution** Vd: at least 28 L Protein binding: approximately 78% **Metabolism** none **Excretion** Renal: approximately 50% Dialyzable: no **Elimination Half Life** exceeds 10 y	Osteoporosis: postmenopausal, due to corticosteroids, and for men Postmenopausal osteoporosis; Prophylaxis	70 mg ORALLY once weekly or 10 mg ORALLY once daily 35 mg ORALLY once weekly or 5 mg ORALLY once daily	**Renal dosing:** Adjustment is NOT necessary for patients with creatinine clearance > 35 ml/min. Avoid use in patients with a creatinine clearance< 35 ml/min. Hepatic dosing: No adjustment

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Calcitonin	Miacalcin, Fortical	**Absorption** IV: time to peak concentration, 16 min to 25 min Nasal: time to peak concentration, 31 min to 39 min Bioavailability: (nasal spray) approximately 3% (range 0.3% to 30.6%) compared to IV **Metabolism** Renal and blood **Excretion** Renal: unchanged hormone and its active metabolite **Elimination Half Life** 43 min	Postmenopausal osteoporosis	100 international units SC or IM every other day OR 200 international units (1 spray) INTRANASALLY per day, alternating nostrils daily	Renal dosing: Not defined Hepatic dosing: Not defined

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Estrogen	Premarin Premarin Intravenous Premphase	**Absorption** Estrone, Oral: time to peak concentration, 6.9 h (25 h) to 8.2 h (58 h) Equilin, Oral: time to peak concentration, 5.6 h (45 h) to 6.8 h (49 h) **Distribution** Estrogen, Vd: widely distributed Estrogen, Protein binding: largely bound **Metabolism** Estrogen-Hepatic; P450 CYP3A4 Metabolites: estrone, estriol, and estrone sulfate **Excretion** Renal **Elimination Half Life** Estrone: 14.8 h (35 h) to 26.7 h (33 h) Equilin: 11.4 h (31 h) to 12.5 h (34 h)	Postmenopausal osteoporosis; Prophylaxis	0.625 mg ORALLY daily given continuously or in cyclical regimens (25 days on, 5 days off)	Renal dosing: Not defined Hepatic impairment Contraindicated

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Etidronate	Didronel	**Absorption** Bioavailability: approximately 3% **Metabolism** not metabolized **Excretion** Fecal: as unchanged Renal: approximately half the dose within 24 h **Elimination Half Life** 165 days	Heterotopic ossification, total hip replacement	20 mg/kg/day ORALLY for 1 month before and 3 months after surgery	**Renal dosing:** In mild-moderate impairment, decrease dose, but no specific guidelines are available. Avoid use in patients with serum creatinine greater than 5 mg/dL **Hepatic dosing:** Not defined
			Hypercalcemia of malignancy	7.5 mg/kg/day administered IV over a period of at least 2 hours on 3 successive days	
			Paget's disease	5-10 mg/kg/day ORALLY, not to exceed 6 months, or 11-20 mg/kg/day, not to exceed 3 months	

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Ibandronate	Boniva	**Absorption** Systemic: Bioavailability: Oral- 0.6%; Effect of food: 90% reduction in bioavailability **Distribution** Vd: 90 L Protein binding: 85.7% to 99.5% **Metabolism** No evidence of drug metabolism **Excretion** Fecal: unabsorbed drug is eliminated in the feces. Renal: 50% to 60% of absorbed dose . **Elimination Half Life** Oral: 10 to 60 h Intravenous: 4.6 to 25.5 hours Postmenopausal women: 37 h to 157 h, dose dependent	Postmenopausal osteoporosis, treatment	2.5 mg ORALLY once daily OR 150 mg ORALLY once monthly OR 3 mg IV every 3 months	**Renal impairment**: Not recommended in patients with CrCl < 30 mL/min **Hepatic dosing**: No adjustment
			Postmenopausal osteoporosis; Prophylaxis	2.5 mg ORALLY once daily or 150 mg ORALLY once monthly	

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Pamidronate	Aredia	**Metabolism** not metabolized **Excretion** Renal: 46% +/- 16% unchanged within 120 h **Elimination Half Life** 28 h +/- 7 h	Bone metastasis, Osteolytic -	90 mg IV administered as a 2-hour infusion every 3-4 weeks; optimal duration of therapy is not known	Renal dosing: Severe impairment: Avoid use Hepatic Dosing: Severe impairment: not defined
			Hypercalcemia of malignancy	60-90 mg IV as a single dose infused over 2 to 24hr	
			Paget's disease (Moderate to Severe)	30 mg IV daily, administered as a 4-hour infusion on 3 consecutive days for a total dose of 90 mg	

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
PTH	Teriparatide, Forteo, Preos	**Absorption** Systemic: Bioavailability: 95% **Distribution** Systemic: Vd: 0.12 L/kg. **Excretion:**90% of endogenous parathyroid hormone is cleared from the plasma by the liver and kidneys Elimination half life: subcutaneous, 1 hr; intravenous, 5 min	Osteoporosis: postmenopausal in women who are at high risk for fracture, and primary or hypogonadal osteoporosis in men	20 micrograms once daily. Efficacy and safety have not been investigated beyond 2 years of treatment	**Renal dosing:** Not defined **Hepatic dosing:** Not defined

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Raloxefine	Evista	**Absorption** Oral: rapid Bioavailability: 2% **Distribution** Vd: 2,583 L/kg (mean) Protein binding: 95% **Metabolism** Hepatic; extensive first-pass, reversible systemic and enterohepatic circulation Metabolites: raloxifene-4'-glucuronide, raloxifene-6-glucuronide and raloxifene-6, 4'-diglucuronide **Excretion** Fecal: primary route of excretion Renal: less than 0.2% unchanged, less than 6% as metabolites **Elimination Half Life** 32.5 h (mean	Postmenopausal osteoporosis	60 mg ORALLY once daily	Renal dosing: Not defined **Hepatic impairment:** Caution advised
			Postmenopausal osteoporosis; Prophylaxis	60 mg ORALLY once daily	

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Risedronate	Actonel	**Absorption** Oral: approximately 1 h Bioavailability: 0.63% Effect of food: intake at 0.5 h and 1 h before breakfast decreases extent of absorption by 55% and 35%, respectively **Distribution** Vd: 6.3 L/kg Protein binding: about 24% **Metabolism** No evidence of systemic metabolism **Excretion** Fecal: unchanged Renal: (Oral), approximately half, primary excretion site Renal: (IV), 85% **Elimination Half Life** 480 h	Osteoporosis: Postmenopausal, or due to corticosteroids	5 mg ORALLY once daily or 35 mg ORALLY once weekly	**Renal dosing:** Avoid use in patients with a creatinine clearance less than 30 mL/min **Hepatic dosing:** No adjustment
			Postmenopausal osteoporosis; Prophylaxis	5 mg ORALLY once daily or 35 mg ORALLY once weekly	

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Tamoxifen		**Absorption** Oral: time to peak concentration, approximately 5 h **Metabolism** Hepatic; P450 CYP3A, CYP2C9 and CYP2D6; extensive Metabolites: N-desmethyl tamoxifen (active metabolite), 4-hydroxytamoxifen and a side chain primary alcohol derivative **Excretion** Fecal: 65%, less than 30% unchanged **Elimination Half Life** about 5 days to 7 days N-desmethyl tamoxifen (active metabolite): approximately 14 days	Breast cancer, Following breast surgery and radiation, to reduce risk of invasive disease - Intraductal carcinoma in situ of breast, reduction in disease incidence in high risk women	20 mg ORALLY daily for 5 years	**Renal dosing**: Not defined Hepatic dosing: Not defined
			Metastatic breast cancer	Metastatic breast cancer: 20-40 mg ORALLY daily	

Drug	Trade Names(s)	Half-life or other relevant pharmacokinetic feature	Labeled indications	Dosing	Dose adjustments for special populations
Zoledronic acid	Zometa	**Excretion** Systemic: Renal: 44% **Elimination Half Life** Systemic: 146 h	Bone metastasis - Multiple myeloma or solid tumor configuration	4 mg IV infused over 15 min every 3- 4 weeks	Renal dosing: Creatinine Clearance 50-60 ml/min: 3.5 mg q 3-4 weeks 40-49 ml/min: 3.3 mg q 3-4 week 30-39 ml/min: 3 mg q 3-4 week <30 avoid use Hepatic dosing: Not defined
			Hypercalcemia of malignancy	4 mg IV infused over 15 min; may repeat in 7 days	

Our outcomes of interest are vertebral, non-vertebral, hip, and radial fractures.

We examine cardiac, dermatologic, endocrine, gastrointestinal, genitourinary, hematological, immunologic, metabolic, musculoskeletal, neurological, psychiatric, and respiratory adverse events. We also examined less serious events such as sweats, fevers, and hot flashes.

Methods

Topic Development and Technical Expert Panel

The topic for this report was nominated in a public process. With input from technical experts, the Scientific Resource Center (SRC) located at Oregon Health Sciences University (OHSU) drafted the initial key questions and, after approval from AHRQ, posted them to a public web site. The public was invited to comment on these questions. After reviewing the public commentary, the SRC drafted final key questions and submitted them to AHRQ for approval.

The key questions subsequently went through several revisions. An original question on whether change in bone density is an adequate intermediate endpoint for treatment effectiveness was removed in October, 2005, based on discussion with AHRQ and our Technical Expert Panel (TEP). In addition, an original question asking for review of practical and validated tools that can be used by patients or clinicians to predict the risk of fracture and the benefits of treatment was declared beyond the scope of this review in December, 2005.

Our TEP met by conference call on October 12, 2005, and January 11, 2006. At the October meeting, the TEP suggested we focus on the bisphosphanates, SERMs, Calcitonin, and PTH. They noted that calcium, Vitamin D, hormones, and exercise had already been reviewed extensively. They suggested that the report summarize existing reviews on these interventions and incorporate study-level data for these interventions only in comparison to agents of primary interest. At the January meeting, due to the amount of literature found and time constraints, we suggested limiting the efficacy analyses to trials with fracture outcomes. The TEP found this acceptable. Thus, we do not analyze intermediate outcomes such as bone mineral density or markers of bone turnover. (The adverse events analyses are not limited to trials reporting fractures.)

The TEP advised us not to pool across different fracture types.

Search Strategy

Our basic search strategy used the National Library of Medicine's Medical Subject Headings (MeSH) key word nomenclature developed for MEDLINE® and was adapted for use in the other databases. We searched MEDLINE® from 1966 to September 2005. The search for the final report will be updated through June, 2006. We also searched the American College of Physicians (ACP) Journal Club database and the Cochrane controlled trials register. The texts of the major search strategies are shown in Appendix A.

To identify systematic reviews, we searched MEDLINE®, the Cochrane Database of Systematic Reviews, the websites of the National Institute for Clinical Excellence, and the NHA Health Technology Assessment Programme. We used results from previously conducted meta-analyses and systematic reviews whenever appropriate.

Our search was not limited by publication type (i.e. randomized controlled trials, systematic reviews). We used terms for osteoporosis, osteopenia, low bone density and both generic and trade names for the drugs listed in the key questions. We also manually searched reference lists of review articles. (We refer to this process as "reference mining.")

We invited TEP members to provide additional studies. In addition, we received the following materials from the Scientific Resource Center:

- Statistical reviews of all FDA-approved drugs listed in the key questions, obtained from the FDA web site;
- Scientific information packets from:
  Auxilium Pharmaceuticals - Testum® (Testosterone)
  Novaritis - Miacalcin® (Calcitonin)
  Merck - Fosamax® (Alendronate)
  Eli Lilly - Evista® (Raloxifine)
  Forteo® (Teriparatide)
  Roche – Boniva® (Ibandronate) and
  Proctor & Gamble - Actonel® (Risedronate)

All citations were imported into an electronic database using ProCite. Citations suggested by stakeholders during the public comment period will be incorporated into our final report.

Study Selection

We developed criteria for inclusion and exclusion based on the patient populations, interventions, and outcome measures specified in the key questions. As suggested by the TEP, we used review articles for information on the effectiveness of estrogen, vitamin D and calcium. We did not search for individual studies of these agents or for exercise; we accepted articles where these agents or exercise were used as comparators with the drugs of interest (the bisphosphanates, SERMs, calcitonin, PTH, and testosterone).

We reviewed titles (and abstracts where available) resulting from our literature search. Full-text articles of potentially relevant articles were retrieved and reviewed for inclusion by two physicians using the "screening" form in Appendix B. The form included the following items, among others.

Population: We included all adult populations. Populations were categorized as men, post-menopausal women, pre-menopausal women, non-white, steroid users, and "other" (not mutually exclusive).

Condition of interest: We included studies of osteopenia, osteoporosis, osteoporosis prevention, or fracture prevention.

Interventions of interest: Bisphosphonates (alendronate, risedronate, etidronate, ibandronate, pamidronate, zolendronic acid), 1-34 PTH; SERMs (raloxefine and tamoxifen).

Comparators of interest: All drugs of interest listed above. Also estrogen, calcium, vitamin D, and exercise.

Outcomes of interest: Studies reporting bone density, bone formation, bone turnover, and fractures were initially accepted. As stated above, in January, 2006, the decision was made to limit outcomes to fractures.

Type of Studies: Studies were categorized as descriptive (historical, editorial, etc.), review/meta-analysis, randomized controlled trial (RCT), controlled clinical trial, trial with open label extension, cohort/case control with at least 1,000 subjects, cohort/case control with less than 1,000 subjects, case report, and "other." We included only RCTs reporting fracture outcomes in our efficacy analyses. We summarized existing systematic reviews and meta-analyses when available. For our adverse event analyses we included both RCTs and observational studies (cohort or case control) of more than 1,000 subjects.

Data Extraction

Using the form included in Appendix B, we extracted the following data from the included RCTs: setting, geographic region, population characteristics (including sex, age, ethnicity, diagnosis), eligibility and exclusion criteria, interventions (dose and duration), concurrent medications or supplements, number screened, eligible, enrolled, and lost to follow-up, method of outcome ascertainment, and type of outcome reported. We also abstracted run-in period and wash-out period where applicable. Data from each article were independently abstracted by two physicians trained in the critical assessment of evidence. They resolved disagreements by consensus; the principal investigator resolved any disagreements that remained after their discussion.

A statistician extracted the fracture outcome data. For each treatment or placebo arm within an RCT, the sample size, and number of persons reporting fractures were extracted.

Adverse events were abstracted by research assistants under the supervision of the statistician. They were recorded onto a spreadsheet that identified each trial group, the description of the adverse event as listed in the original article, and the number of subjects in each group. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. If a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume zero events occurred unless the trial report specifically stated that zero events were observed. By taking this approach, we may have overestimated the number of patients for whom a particular adverse event was observed.

Per the Scientific Resource Center, we abstracted the aims, time period covered, eligibility criteria, study designs included, interventions studied, populations, and results from systematic reviews and meta-analyses. These data are presented in the evidence tables (Appendix C).

Quality Assessment

We used predefined criteria to assess the quality of systematic reviews and individual RCTs. As observational studies were not used for efficacy analyses, we felt that quality rating was unnecessary.

Before we assessed the quality of systematic reviews and meta-analyses, we reviewed the QUOROM statement,[10] which consists of a checklist of 18 items and a flow diagram. The statement's authors were able to identify scientific evidence for only eight items. As the authors did not suggest a specific scoring mechanism for the checklist, we focused on aspects of internal and external validity as suggested in the Medicare Modernization Act (MMA) Drug Review Methods Manual distributed in March, 2005. These items, which include search strategy, inclusion criteria for individual studies, and method of synthesis, among others, are presented in the evidence table for systematic reviews in Appendix C. Each systematic review or meta-analyses is discussed in detail in its corresponding section of the results.

We assessed the quality of individual RCTs using the Jadad scale, which was developed for drug trials and which we feel is well suited to the evaluation of quality in this report. The Jadad scale ranges from 0-5 based on points given for randomization, blinding, and accounting for withdrawals and dropouts.[11] Across a broad array of meta-analyses, an evaluation found that studies scoring 0-2 report exaggerated results compared to studies scoring 3-5.[12] The latter have been called "good" quality and the former called "poor" quality.

Applicability

Effectiveness studies compare a new drug with viable alternatives rather than with placebos and produce health, quality of life, and economic outcomes data under real world conditions. For example, an effectiveness trial of a new asthma drug would include asthma-related emergency room visits, the frequency and costs of physician visits, patients' quality of life, patient compliance with the medications, acquisition costs of the medications, and frequency and costs of short-term and long-term adverse events."[13]

Clinicians and policymakers often distinguish between the efficacy of an intervention (the extent to which the treatment works under ideal circumstances) and the effectiveness of the intervention (the extent to which the treatment works on average patients in average settings). Efficacy studies tend to be smaller, to be performed on referred patients and in specialty settings, and to exclude patients with comorbidities. Effectiveness studies are larger and more generalizable to practice. Please be aware that the vast majority of studies included in our report are efficacy studies. However, effectiveness studies are included in our analyses of adverse events.

Rating the body of evidence

We assessed the overall strength of evidence for outcomes using a method developed by the Grade Working Group, which classified the grade of evidence across outcomes according to the following criteria:[14]

- **High** = Further research is very unlikely to change our confidence on the estimate of effect.
- **Moderate** = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low** = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Very Low** = Any estimate of effect is very uncertain.

Data Synthesis

The primary outcome for our efficacy analysis is the number of people who reported at least one fracture. Because the occurrence of a fracture was fairly rare, and zero events were often observed in at least one of the treatment groups, odds-ratios (OR) were calculated using the Peto method.[15] An OR with a value less than one indicates that the odds of having a fracture is less in the intervention group than in the comparison group. Trials that report zeros in both groups have an undefined OR. Because fractures are rare events, the OR approximates the relative risk (RR) of fracture.

For comparisons that had at least three trials and that were judged to be clinically similar to warrant meta-analysis, we estimated a pooled OR using the Peto method.[15] When analyzing outcomes with rare events, the Peto method has been shown to give the least biased estimate.[16] Forest plots are provided when trials were pooled. The OR for each trial is illustrated by a box, where the size of the box is inversely proportional to the trial's sample size. The 95% confidence interval (CI) is depicted as a horizontal line on each side of the box. A diamond on the bottom of each graph represents the pooled estimate and CI. A vertical solid line at one indicates no treatment effect.

We also report the chi-squared test of heterogeneity p-value based on Cochran's Q[17] and the I-squared statistic.[18] A significant Q statistic or I^2 values close to 100% represent very high degrees of heterogeneity. I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity.

All efficacy meta-analyses were conducted with Stata statistical software.[19]

We also provide narrative summaries of evidence where applicable.

Adverse events

For the analysis of adverse events, we examined six comparisons: 1) drugs within the same class (i.e. bisphosphonate vs bisphosphonate) 2) BD drugs from two different classes (i.e. bisphosphonate vs SERM); 3) BD drugs vs estrogen; 4) BD drugs vs vitamin D; 5) BD drugs vs calcium; 6) BD drugs vs placebo/control.

A physician grouped adverse events into various categories and subcategories. For groups of events that occurred in two or more trials, we performed a meta-analysis to estimate the pooled OR and its associated 95% confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analyses using the statistical software package StatXact Procs for SAS Users.[20] For events that were reported in only one trial, an OR is calculated and reported.

Any significant OR greater than one indicates the odds of the adverse event associated with the bone density drug is larger than the odds associated with being in the comparison (placebo, vitamin D, estrogen, calcium, or other bone density drug) group. We note that if no events were observed in the comparison group, but events were observed in the intervention group, the OR is infinity and the associated confidence interval is bounded from below only. In such a case, we report the lower bound of the confidence interval.

Peer Review

This draft report was submitted for peer review and public comment in May, 2006. Feedback will be incorporated into the final version later this year. A list of reviewers comments and author responses will be included as Appendix D.

Results

We identified 1,533 titles through our electronic library searches, 97 titles through scientific information packets from pharmaceutical companies, 451 titles through reference mining, and five titles through experts, for a total of 2,086 titles. After reviewing titles and / or abstracts where available, we ordered 1,558. We were unable to obtain seven.

Of the 1,552 articles screened, 1,490 were rejected for the reasons detailed in Figure 1. Appendix E contains a list of excluded studies. Because systematic reviews already existed for alendronate, risedronate, etidronate, raloxefine, calcitonin, PTH, and estrogen, we did not re-analyze trials of these drugs versus placebo in our efficacy analyses. This means that 198 articles on randomized controlled trials were excluded from further efficacy analyses. In total, 45 RCTs and 15 meta-analyses were considered for the efficacy analyses. Seven of these articles reported on the same trial as others, two were later rejected because they were dosage studies of one drug, and two more were rejected because the randomization was deemed inadequate by our investigators. Thus, a total of 34 RCTs were left for inclusion.

We submitted a draft report in May, 2006. At that time, we were asked by AHRQ to include an additional systematic review and several additional RCTs. These are not reflected in Figure 1.

Figure 1. Literature Flow

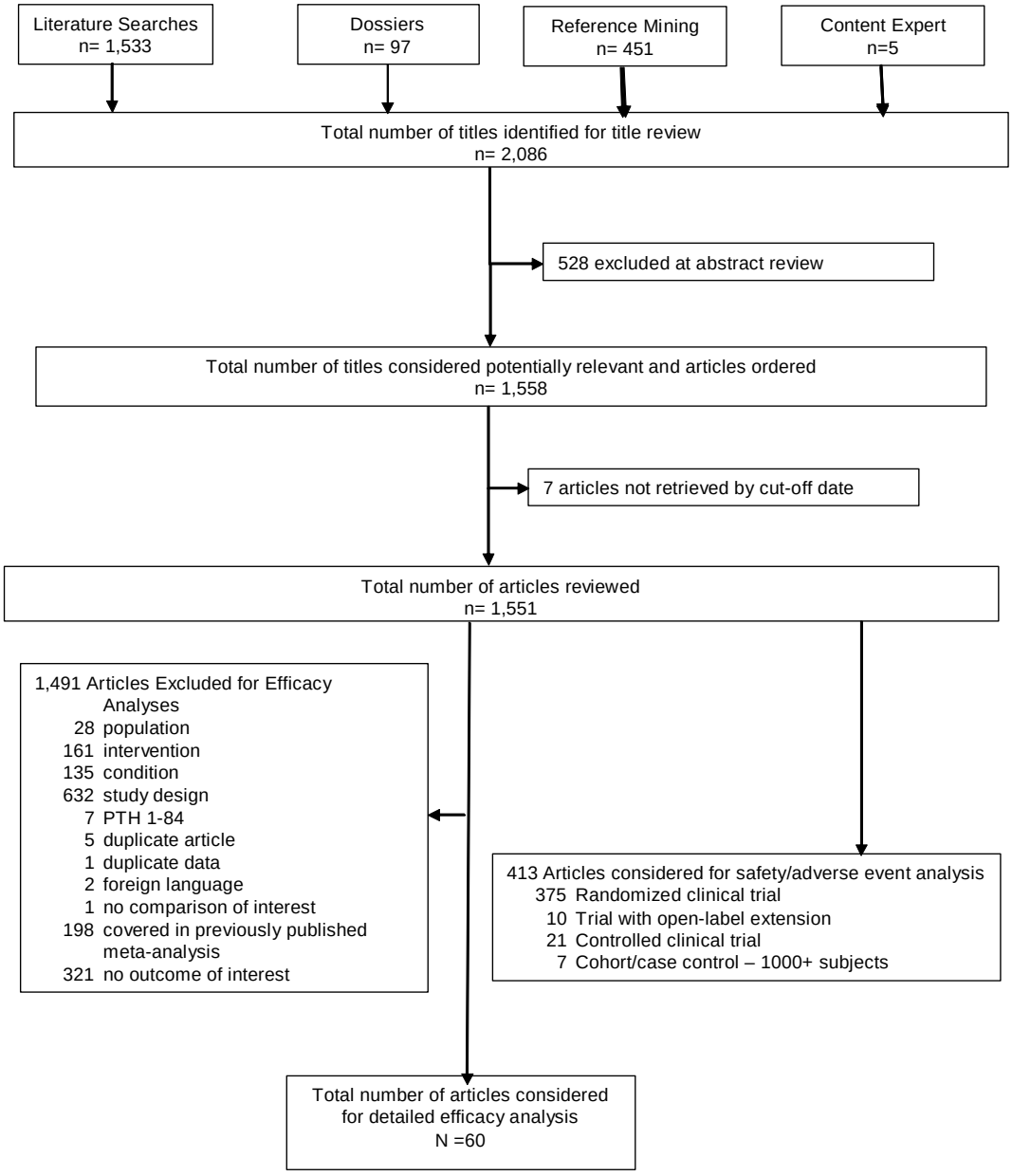
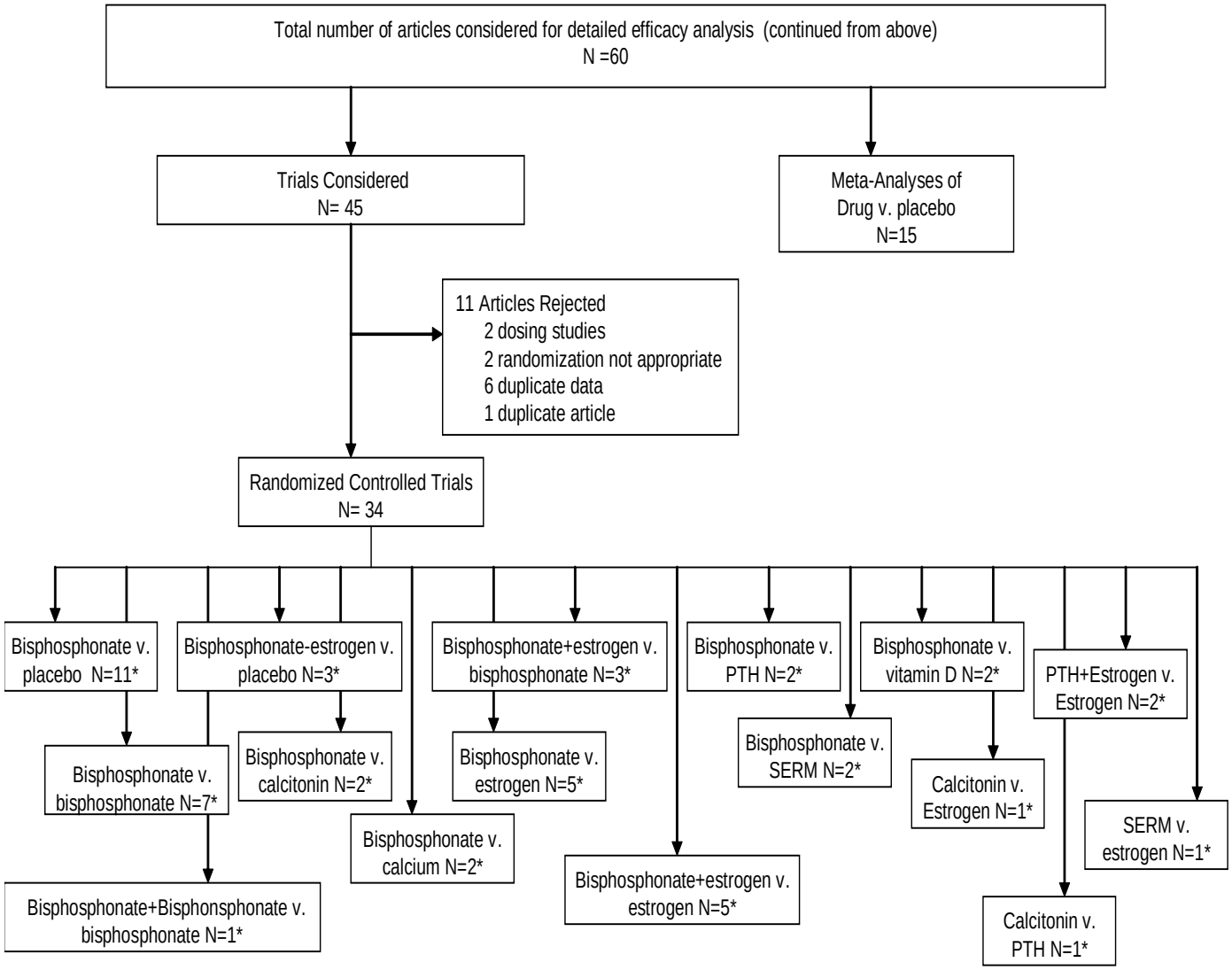


Figure 1. Literature Flow (continued)



*articles considered are not mutually exclusive

For the 34 accepted trials, mean Jadad score was 2.65. Mean age of subjects in the trials was 60.7 years. Length of treatment ranged from six to 48 months; mean was 22 months. Funding sources were reported in 27 of the articles; 20 of these were at least partially funded by pharmaceutical companies.

Our analyses of adverse events included 413 articles, representing 375 randomized controlled trials, 21 other controlled clinical trials, ten open-label trials, and seven observational studies (case control or cohort) with 1,000 or more subjects.

Key Question 1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone-density:

- Bisphosphonate medications, specifically: alendronate, risedronate, etidronate, ibandronate, pamidronate, and zoledronic acid
- Calcitonin
- Calcium
- Estrogen for women
- PTH
- Selective estrogen receptor modulators (SERMs), specifically: raloxifene and tamoxifen
- Testosterone for men
- Vitamin D
- Combinations of above
- Exercise in comparison to above agents

Key Points

- There is good evidence from RCTs that, compared with placebo, alendronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxefine prevent vertebral fractures.
- There is evidence from one RCT that compared with placebo 1-34 PTH prevents non-vertebral fractures.
- There is good evidence from RCTs that compared with placebo; risedronate prevents both non-vertebral and hip fractures.
- There is good evidence from RCTs that, compared with placebo, alendronate prevents both non-vertebral and hip fractures.

- Based on limited data, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any agent.
- Based on the Women's Health Initiative but not on prior meta-analyses, estrogen is associated with a reduced incidence of hip fractures.
- Based on limited data, superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates in comparison to calcitonin, calcium or raloxefine. However, these studies were not designed or powered to detect fractures.
- Based on a large body of evidence, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison to estrogen.
- There are no data from RCTs on the effect of testosterone on the prevention of fractures.
- There are no data from RCTs on the effect of exercise relative to agents used to treat or prevent osteoporosis on fracture prevention.

Detailed Analyses

Drug vs. Placebo Comparisons

For 9 of the 14 agents for the prevention or treatment of osteoporosis that were reviewed in this report, we identified 15 meta-analyses that described the effect of the agent relative to placebo on fracture incidence.[21-35] For 3 of the 14 agents not covered by existing meta-anayses (ibandronate, pamidronate and zolendronic acid) we identified 11 RCTs that described the effect of the agent relative to placebo on fracture incidence.[36-46] For 2 of the 14 agents (tamoxifen and testosterone) we did not identify any meta-analyses or RCTs that described the effect of the agent relative to placebo on fracture incidence.

The risk of developing fracture relative to placebo for the 12 agents for which data are available is summarized in Figures 2-5 and in the text that follows.

Figure 2. Risk of vertebral fractures for agents used to treat or prevent osteoporosis relative to placebo.

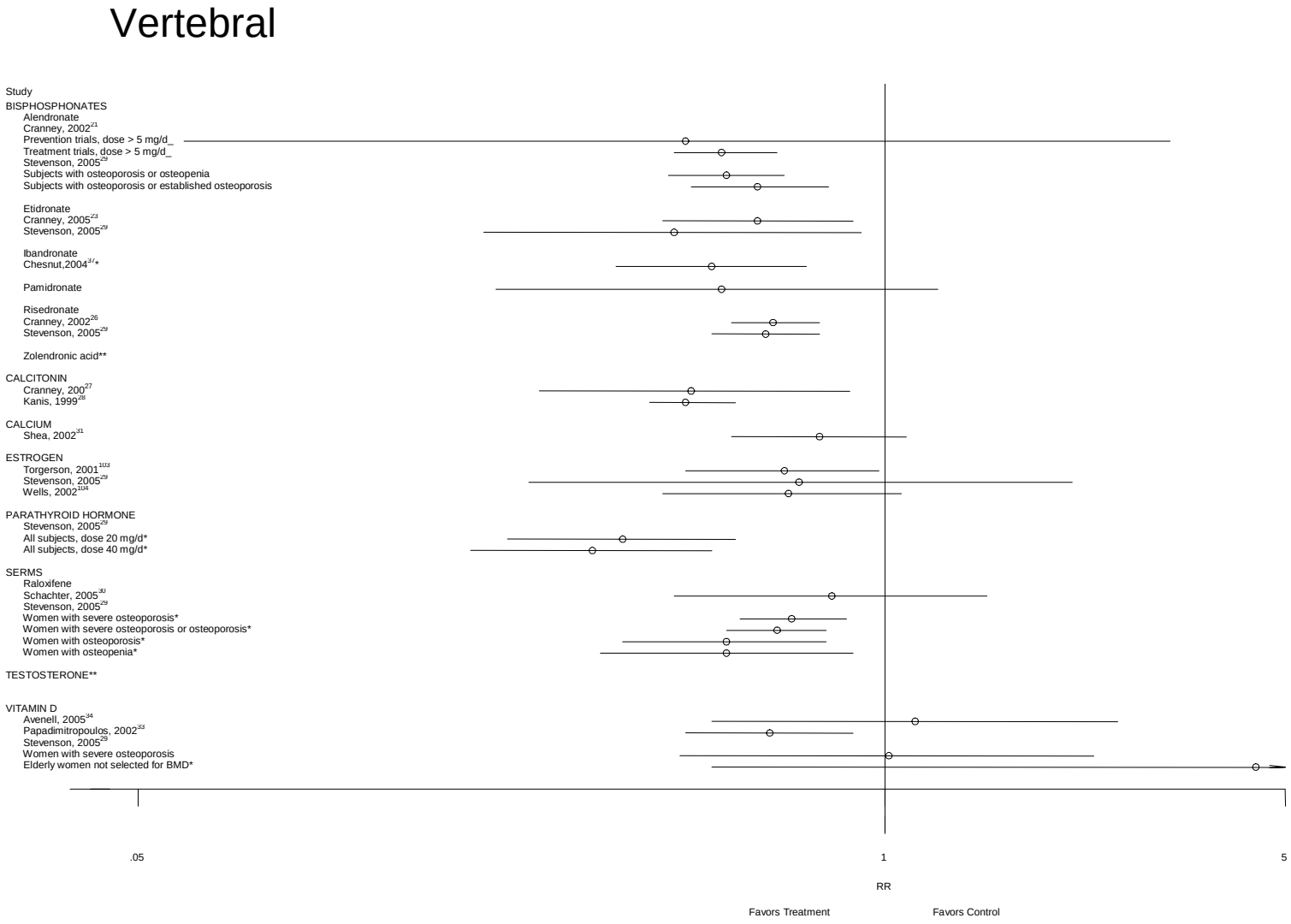


Figure 3. Risk of non-vertebral fractures for agents used to treat or prevent osteoporosis relative to placebo.

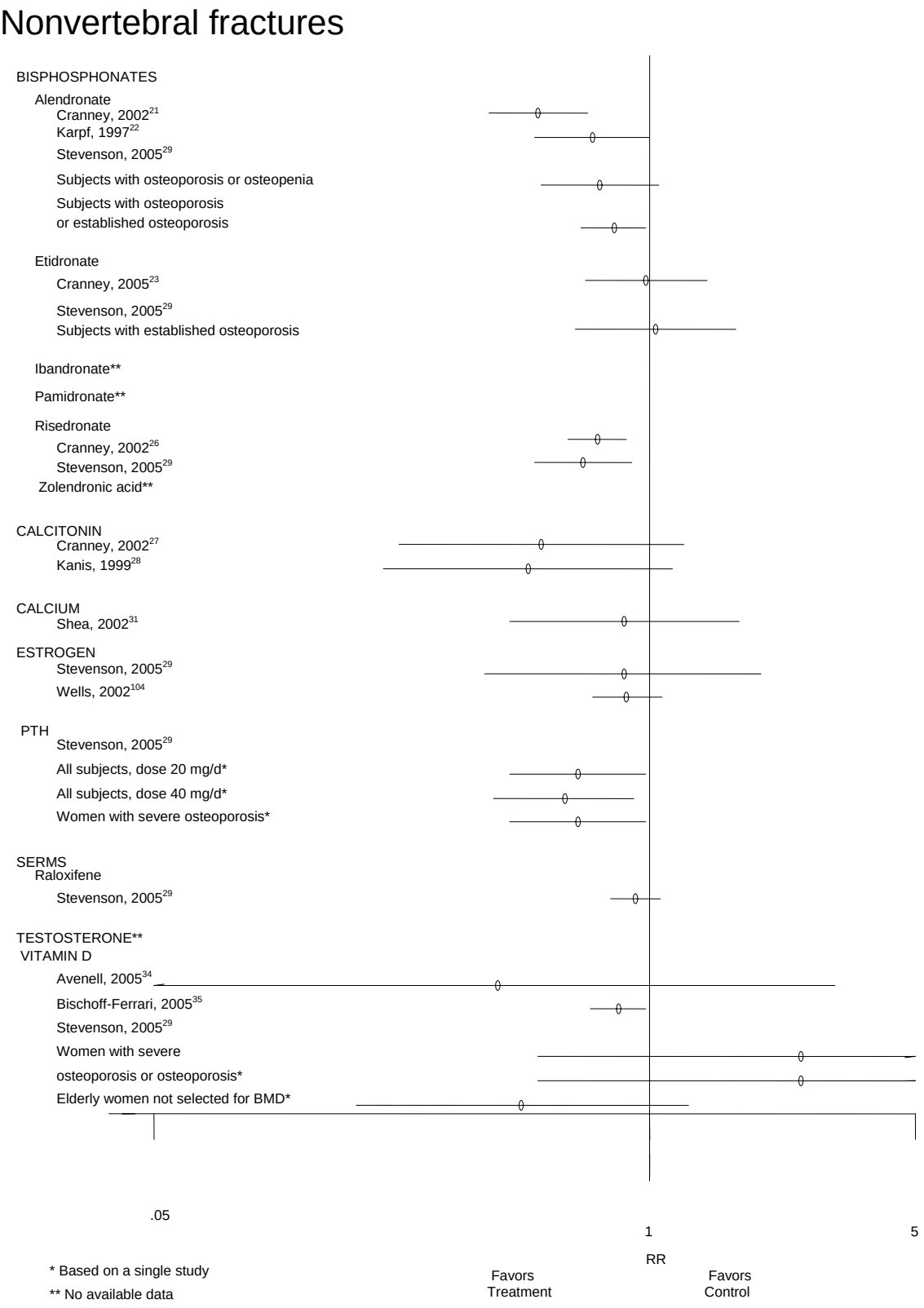


Figure 4. Risk of hip fractures for agents used to treat or prevent osteoporosis relative to placebo.

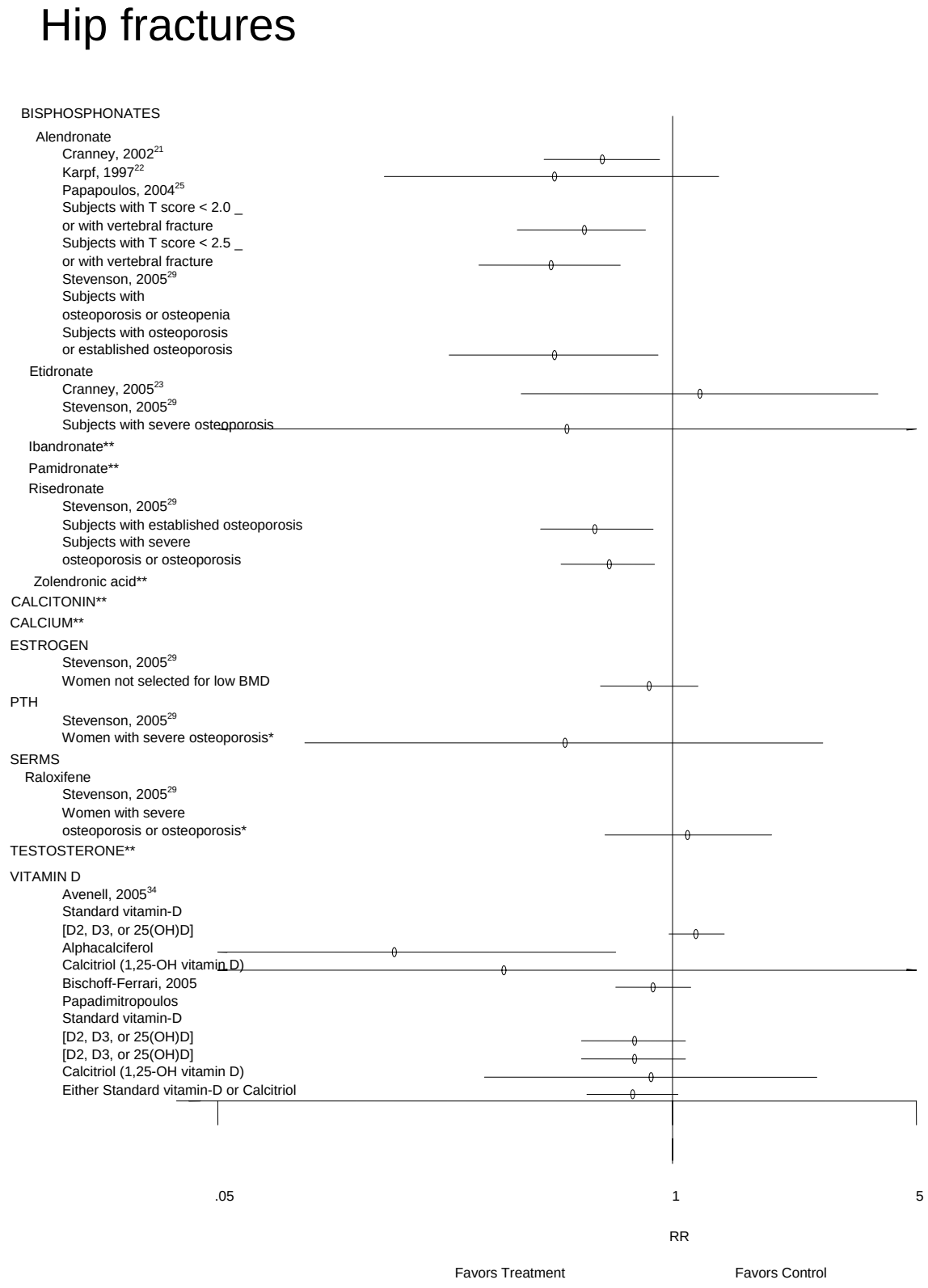
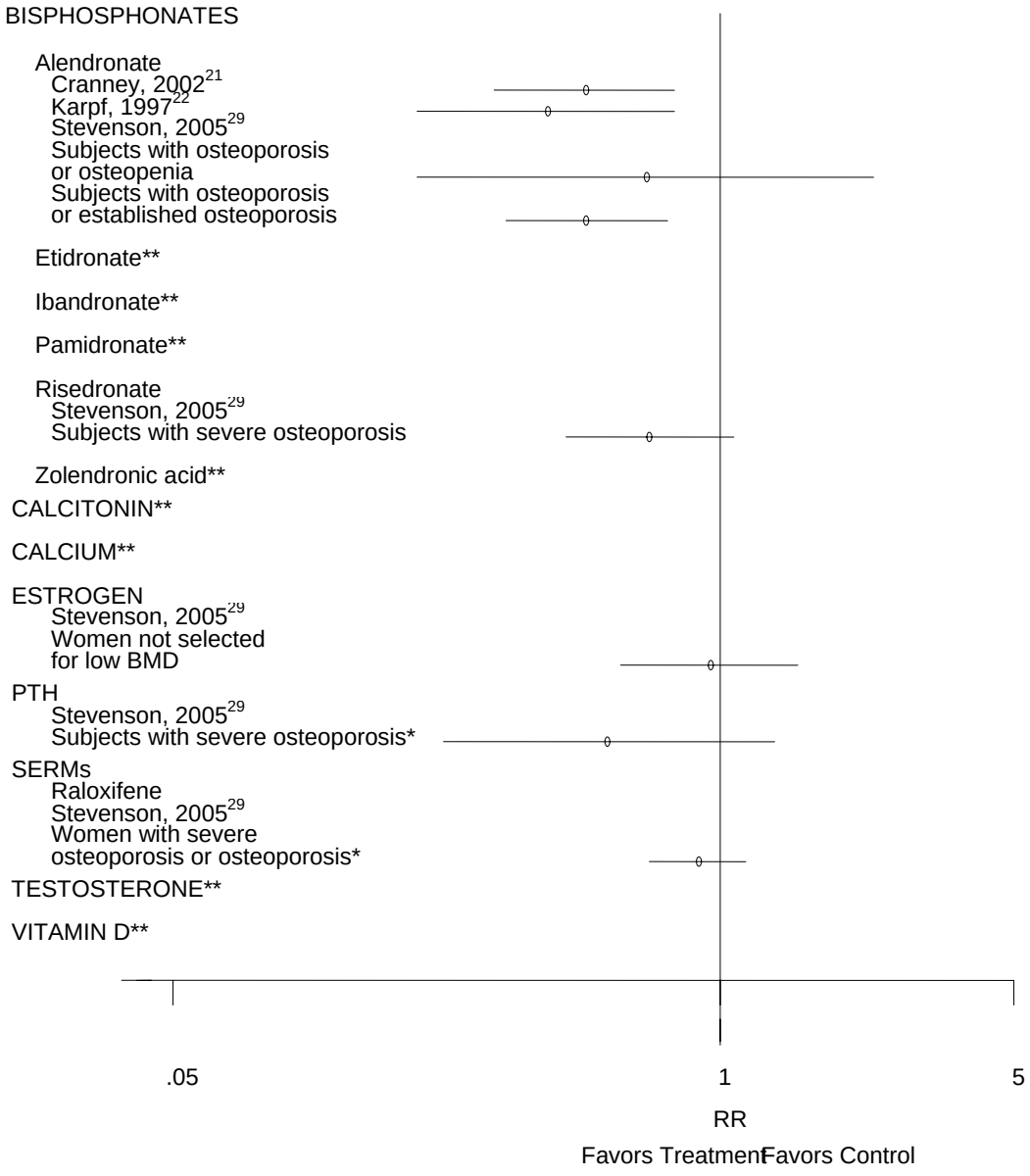


Figure 5. Risk of wrist fractures for agents used to treat or prevent osteoporosis relative to placebo.

Wrist fractures



Bisphosphonates

Alendronate:

We identified four meta-analyses[21, 22, 25, 29] that pooled data from 14 different RCTs to estimate the effect of alendronate on fracture risk reduction relative to placebo or no treatment among postmenopausal women. The studies that were included in each of the meta-analyses are detailed in Table 2. These meta-analyses reported pooled risk estimates for vertebral, non-vertebral, hip and wrist fractures (Table 3).

Table 2. Randomized controlled trials included in meta-analyses of effect of alendronate on fracture relative to placebo or no treatment, by fracture type.*

RCTs (Author, year)	Meta-analysis (Author, year)											
	Cranney, 2002[21]				Karpf, 1997[22]			Papapoulos, 2004[25]	Stevenson, 2005[29]			
	Fracture type*											
	V	NV	H	W	NV	H	W	H	V	NV	H	W
Adami, 1995[47]	X	X			X	X	X					
Black, 1996[48]	X	X	X	X				X	X	X	X	X
Bone, 1997[49]	X	X										
Bonnick, 1998[50]		X						X				
Chesnut, 1995[51]	X	X			X	X	X					
Cummings, 1998[52]	X	X						X	X		X	X
Dursun, 2001[53]									X			
Greenspan, 1998[54]								X				
Hosking, 1998[55]	X	X										
Liberman, 1995[56]	X	X			X	X	X	X	X	X	X	X
McClung, 1998[57]	X	X										
Pols, 1999[58]		X								X		
Unpublished data					X	X	X					
Weinstein, 1994[59]					X	X	X					

*V=vertebral, NV=non-vertebral, H=hip, W=wrist/forearm; X= Included in pooled analysis.

Table 3. Pooled risk estimates of fracture for alendronate, relative to placebo or no treatment, among postmenopausal women.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral				
Cranney, 2002[21]				
Prevention trials, dose ≥ 5 mg/d	2	1,355	0.45	(0.06, 3.15)
Treatment trials, dose ≥ 5 mg/d	7	8,005	0.53	(0.43, 0.65)
Stevenson, 2005[29]				
Subjects with osteoporosis or osteopenia	2	2,827	0.53	(0.42, 0.67)
Subjects with osteoporosis or established osteoporosis	3	5,093	0.60	(0.46, 0.80)
Non-vertebral				
Cranney, 2002[21]				
All trials, 5 mg/d	8	8,603	0.87	(0.73, 1.02)
All trials, 10-40 mg/d	6	3,723	0.51	(0.38, 0.69)
Treatment trials, 10-40 mg/d			0.51	(0.38, 0.69)
Karpf, 1997[22]	5	1,602	0.71	(0.50, 1.00)
Stevenson, 2005[29]				
Subjects with osteoporosis or osteopenia	3	6,626	0.74	(0.52, 1.06)
Subjects with osteoporosis or established osteoporosis	2	3,021	0.81	(0.66, 0.98)
Hip				
Cranney, 2002[21]				
All trials, 5 mg/d	8	8,603	0.70	(0.46, 1.05)
All trials, 10-40 mg/d	6	3,723	0.45	(0.18, 1.13)
All trials, 5-40 mg/d	11	11,808	0.63	(0.43, 0.92)
Karpf, 1997[22]	5	1,602	0.46	(0.15, 1.36)
Papapoulos, 2004[25]				
Subjects with T score ≤ 2.0 or with vertebral fracture	6	9,023	0.55	(0.36, 0.84)
Subjects with T score ≤ 2.5 or with vertebral fracture	6	6,804	0.45	(0.28, 0.71)
Stevenson, 2005[29]				
Subjects with osteoporosis or osteopenia	2	5,426	0.68	(0.30, 1.54)
Subjects with osteoporosis or established osteoporosis	2	3,021	0.46	(0.23, 0.91)
Forearm/Wrist				
Cranney, 2002[21]				
All trials, 5 mg/d	8	8,603	0.84	(0.51, 1.40)
All trials, 10-40 mg/d	6	3,723	0.48	(0.29, 0.78)
Karpf, 1997[22]	5	1,602	0.39	(0.19, 0.78)
Stevenson, 2005[29]				
Subjects with osteoporosis or osteopenia	2	5,426	0.67	(0.19, 2.32)
Subjects with osteoporosis or established osteoporosis	2	3,071	0.48	(0.31, 0.75)

Etidronate:

We identified two meta-analyses[23, 29] that pooled data from ten different RCTs to estimate the effect of etidronate on fracture risk reduction relative to placebo or no treatment among post-menopausal women (Table 4). These meta-analyses reported pooled risk estimates for vertebral, non-vertebral, hip and wrist fractures (Table 5).

Table 4. Randomized controlled trials included in meta-analyses of effect of etidronate on fracture relative to placebo or no treatment.

RCTs (Author, year)	Meta-analyses (Author, year)					
	Cranney, 2001[23]			Stevenson, 2005[29]		
	Fracture type*					
	V	NV	H	V	NV	H
Herd, 1997[60]	X					
Iwamoto, 2001[61]					X	
Lyritis, 1997[62]	X	X	X	X	X	X
Meunier, 1997[63]	X	X				
Montessori, 1997[64]	X	X				
Pacifici, 1988[65]	X					
Pouilles, 1997[66]	X	X				
Storm, 1990[67]	X	X	X		X	
Watts, 1990[68]	X	X	X	X	X	X
Wilmalawansa, 1998[69]	X	X			X	

*V=vertebral, NV=nonvertebral, H=hip, W=wrist/forearm; X= Included in pooled analysis.

Table 5. Pooled risk estimates of fracture for etidronate, relative to placebo or no treatment, among post-menopausal women.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Cranney, 2001[23]				
All trials	10	1,076	0.60	(0.41, 0.88)
Prevention trials	5	738	0.61	(0.29, 1.26)
Treatment trials	5	338	0.59	(0.38, 0.94)
Stevenson, 2005[29]				
Subjects with established osteoporosis	2	263	0.43	(0.20, 0.91)
Non-vertebral				
Cranney, 2001[23]				
All trials	8	867	0.98	(0.68, 1.42)
Prevention trials	4	586	1.05	(0.69, 1.60)
Treatment trials	4	281	0.75	(0.34, 1.70)
Stevenson, 2005[29]				
Subjects with established osteoporosis	4	410	1.04	(0.64, 1.69)
Hip				
Cranney, 2001[23]				
All trials	4	589	1.20	(0.37, 3.88)
Stevenson, 2005[29]				
Subjects with severe osteoporosis	1	309	0.50	(0.05, 5.34)

Ibandronate:

We identified four RCTs[37, 38, 40, 42] that reported the effects of ibandronate relative to placebo or control on the incidence of fractures. The study population in three of these studies was postmenopausal women with osteoporosis or osteopenia.[37, 38, 42] The study population in the other study was male and female kidney transplant recipients.[40] In two of these studies, fracture prevention was the primary outcome and the studies had sufficiently large sample sizes to detect differences in fracture risk among study groups.[37, 38] In the other two studies,[40, 70] fracture data were reported as adverse events among samples not large enough to detect differences in fracture rates among study groups.

Among the studies that evaluated fracture risk as a primary outcome, one assessed the effect of daily and intermit ibandronate on vertebral (primary outcome) and non-vertebral fractures (secondary outcome) among 1,952 subjects.[37] In this study the risk of clinical vertebral fractures for daily and intermittent ibandronate relative to placebo were the same, 0.54 (95% CI, 0.32, 0.88). The relative risk of clinical non-vertebral fractures for daily and intermittent ibandronate relative to placebo were 1.0 (95% CI, 0.73, 1.36) and 1.09 (95% CI, 0.80, 1.50), respectively. The other study found no association between ibandronate and morphometric vertebral fractures among 2,862 subjects.[38]

Among the studies that reported fracture data as adverse events, one was performed among 60 post-menopausal women[42] and the other among 80 kidney transplant recipients.[40] The data

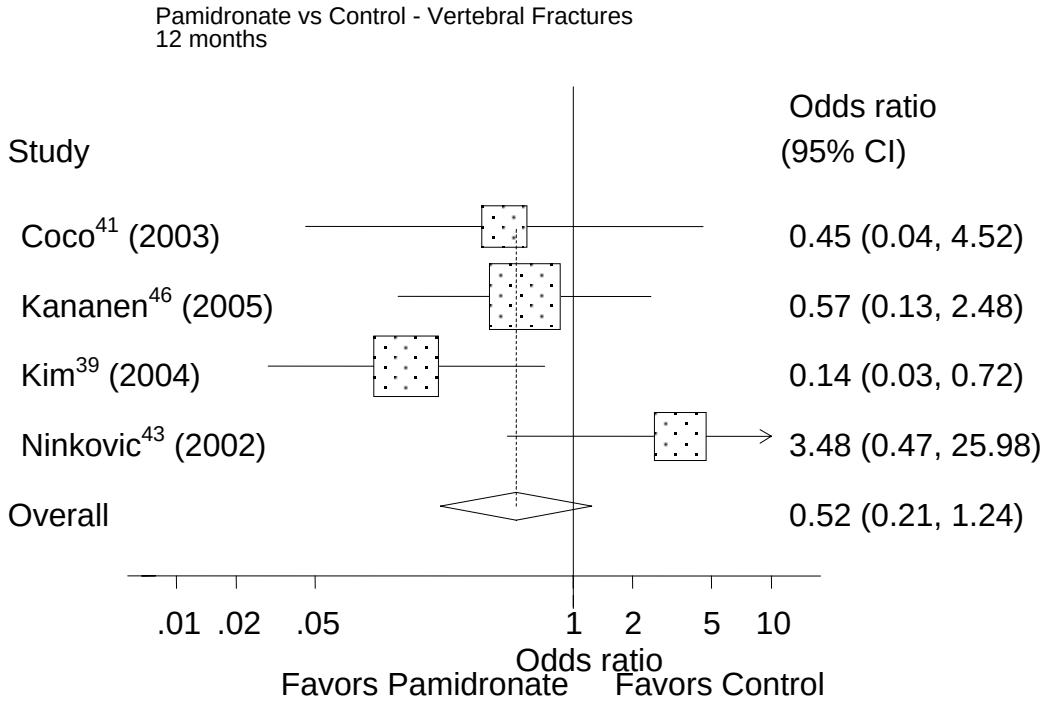
reported in these studies did not demonstrate an association between ibandronate and either arm or vertebral fractures, but were not powered to do so.

Pamidronate:

We identified six RCTs[39, 41, 43-46] that reported the effects of pamidronate relative to placebo or control on the incidence of fractures. Four of these studies were performed among male and female organ transplant recipients,[41, 43, 44, 46] one among men or women receiving chemotherapy for lymphoma[39] and one among postmenopausal women with osteoporosis or osteopenia.[45] The occurrence of new fractures was a secondary outcome in all of the studies. These studies reported the following types of fractures: hip, long bone, non-vertebral and vertebral. In the one study that assessed hip fractures, none occurred in either the pamidronate or control groups.[41] Relative to control, there was no significant association between pamidronate and long bone fractures (OR 0.48, 95 % CI 0.11, 2.17). Likewise, relative to placebo, there was no significant association between pamidronate and non-vertebral fractures (OR 1.21, 95 % CI 0.07, 19.96). However, none of the studies had sample sizes large enough to detect a difference in fracture rates between groups.

There were sufficient data to perform a pooled analysis only of vertebral fractures. Among four studies[39, 41, 43, 46], the pooled odds of vertebral fractures for pamidronate relative to placebo or control among 269 subjects was 0.52 (95% CI, 0.21, 1.24). However, this pooled sample size is not large enough to detect a difference in fracture rates study groups (Figure 6). There are no data on use of pamidronate for postmenopausal osteoporosis.

Figure 6. Pooled risk of vertebral fractures for pamidronate relative to placebo or control among subjects with organ transplants or undergoing chemotherapy.



Author, year	Population	Fracture ascertainment	Sample size	OR	95% CI
Coco, 2003[41]	Renal transplant recipients	Secondary outcome	59	0.45	0.04, 4.52
Kananen, 2005[46]	Allogenic stem cell recipients	Secondary outcome	66	0.57	0.13, 2.48
Kim, 2004[39]	Lymphoma patients receiving chemotherapy	Secondary outcome	45	0.14	0.03, 0.72
Ninkovic, 2002[43]	Liver transplant recipients	Secondary outcome	99	3.48	0.47, 25.98
Peto pooled OR			269	0.52	0.21, 1.24

Heterogeneity chi-squared = 5.92 (d.f. = 3) p = 0.116
I-squared (variation in OR attributable to heterogeneity) = 49.3%

Risedronate:

We identified two meta-analyses[26, 29] that pooled data from eight different RCTs to describe the effect of risedronate on fracture risk reduction relative to placebo or no treatment, among post-menopausal women. The studies that were included in each of the meta-analyses are detailed in

Table 6. These meta-analyses reported pooled risk estimates for vertebral, non-vertebral, hip, and wrist fractures (Table 7).

Table 6. Randomized controlled trials included in meta-analyses of effect of risedronate on fracture relative to placebo or no treatment.

RCTs (Author, year)	Meta-analyses (Author, year)					
	Cranney, 2002[26]		Stevenson, 2005[29]			
	Fracture Type					
	Vertebral	Non-vertebral	Vertebral	Non-vertebral	Hip	Wrist
Clemmensen, 1997[71]	X	X				
Fogelman, 2000[72]	X	X				
Harris, 1999[73]	X	X	X	X	X	X
McClung, 1998[74]* McClung 1998[74]*		X				
McClung, 2001[75]		X			X	
McClung, 2001[75]		X				
Mortensen, 1998[76]	X	X				
Reginster, 2000[77]	X	X	X	X	X	X

X= Included in pooled analysis; *same study reported in two different abstracts.

Table 7. Pooled risk estimates of fracture for risedronate, relative to placebo or no treatment, among post-menopausal women.

Type of fracture	**# studies**	**Sample size**	RR	(95% CI)
Vertebral				
Cranney, 2002[26]	5	2,604	0.64	(0.54, 0.77)
Stevenson, 2005[29]	2	2,064	0.62	(0.50, 0.77)
Non-vertebral				
Cranney, 2002[26]	7	12,958	0.73	(0.61, 0.87)
Stevenson, 2005[29]	2	2,439	0.67	(0.50, 0.90)
Hip				
Stevenson, 2005[29]				
Subjects with established osteoporosis	3	4,142	0.60	(0.42, 0.88)
Subjects with severe osteoporosis or osteoporosis	3	7,884	0.66	(0.48, 0.89)
Wrist				
Stevenson, 2005[29]				
Subjects with severe osteoporosis	2	2,439	0.68	(0.43, 1.08)

Zolendronic acid:

We identified one RCT[36] that reported the effect of zolendronic acid relative to placebo on the incidence of vertebral and non-vertebral fractures among postmenopausal women. In this study 351 postmenopausal women were randomized to different doses and frequencies of zolendronic acid ranging from 1-4 grams given in 1-4 doses over a one-year period. Fracture incidence was a secondary outcome in this study. Among 59 subjects randomized to placebo and 292 subjects randomized to zolendronic acid, none sustained vertebral fractures during the 1-year study period. There were five non-vertebral fractures in each the zolendronic acid and placebo groups. There was no significant association between any dose of zolendronic acid and non-vertebral fractures relative to placebo (Table 8). However, this study does not have sufficient statistical power to detect differences in fracture among study arms.

Table 8. Non-vertebral fractures with zolendronic acid relative to placebo, by dose and frequency among post-menopausal women.

Dose and frequency	Number of fractures, Zolendronic acid	Number of fractures, placebo	Odds ratio (95% CI)
4 grams once	1/60	1/59	0.98 (0.06, 15.91)
2 grams every 6 months	1/61	1/59	0.97 (0.06, 15.65)
0.25 grams every 3 months	0/60	1/59	0.13 (0.00, 6.71)
0.5 grams every 3 months	1/58	1/59	1.02 (0.06, 16.46)
1 gram every 3 months	2/53	1/59	2.2 (0.22, 21.7)

Calcitonin

We identified three meta-analyses[24, 27, 28] that describe the effect of calcitonin on fracture risk reduction relative to placebo or no treatment. Since one[27] is an update of another[24], we describe only the more recent[27] of those two. The RCTs included in these meta-analyses are detailed in Table 9. These meta-analyses reported pooled risk estimates for vertebral and non-vertebral fractures (Table 10). One of the meta-analyses was restricted to postmenopausal women,[27] the other was not restricted to a specific population and included postmenopausal women, men and women with osteoporosis, as well as men and women taking coricosteroids.[78]

Table 9. Randomized controlled trials included in meta-analyses of effect of calcitonin on fracture relative to placebo or no treatment.

RCTs (Author, year)	Meta-analyses (Author, year)			
	Cranney, 2002[27]		Kanis, 1999[28]	
	Vertebral	Non-vertebral	Vertebral	Non-vertebral
Arnala, 1996[79]			X	X
Agrawal, 1980[80]			X	X
Chesnut, 2000[81]	X	X		
Gennari, 1985[82]			X	
Gruber, 1984[83]			X	
Healey, 1996[84]			X	
Hizmetli, 1996[85]	X			
Overgaard, 1992[86]	X	X	X	X
Peyron, 1980[87]			X	
Rico, 1992[88]			X	X
Rico, 1995[89]		X	X	
Ringe, 1990[90]			X	X
Ringe, 1987[91]			X	X
Sambrook, 1993[92]			X	X
Stock, 1997[93]			X	
Luengo, 1994[94]			X	X

X=Included in pooled analysis.

Table 10. Pooled risk estimates of fracture for calcitonin relative to placebo or no treatment.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral				
Cranney, 2002[27]	4	1,404	0.46	(0.25, 0.87)
Kanis, 1999[28]	10	1,744	0.80	(0.64, 1.01)
Non-vertebral				
Cranney, 2002[27]	3	1,481	0.52	(0.22, 1.23)
Kanis, 1999[28]	10	1,744	0.48	(0.20, 1.15)

Calcium

We identified one meta-analysis[31] and one RCT[95] published after the meta-analysis that describe the effect of calcium supplementation on fracture risk reduction relative to placebo or no treatment, among post-menopausal women. The meta-analysis pooled data from five different RCTs (Table 11). Vitamin D was given to all subjects in one of the studies (single 300,000 iu dose at study inception).[96] Vitamin D was not used in any of the other studies. This meta-analysis reported pooled risk estimates for vertebral and non-vertebral fractures, neither of which were statistically significant (Table 12).

In the recent RCT, 1,460 community-dwelling women 70 years or older were randomized to calcium carbonate, 600 mg twice per day, or placebo for 5 years. Clinical incident osteoporotic fractures was a primary endpoint and the study had a large enough sample size to detect differences in fracture rates across study arms. In total, 16.1% of the study population sustained one or more clinical osteoporotic fractures during the study period. In the intention-to-treat analysis, calcium supplementation did not significantly reduce fracture risk (hazard ratio, 0.87; 95% CI, 0.67-1.12). However, 830 patients (56.8%) who took 80% or more of their tablets (calcium or placebo) per year had reduced fracture incidence in the calcium compared with the placebo groups (10.2% vs 15.4%; hazard ratio, 0.66; 95% CI, 0.45-0.97).

Table 11. Randomized controlled trials included in meta-analysis of effect of calcium on fracture relative to placebo or no treatment.

Meta-analyses (Author, year)		
RCTs (Author, year)	Shea, 2002[31]	
	Vertebral	Non-vertebral
Chevally, 1994[96]	X	X
Hansson, 1987[97]	X	
Recker, 1996[98]	X	
Reid, 1993[99]	X	
Riggs, 1998[100]	X	X

X= Included in pooled analysis;

Table 12. Pooled risk estimates of fracture for calcium relative to placebo or no treatment among post-menopausal women.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures Shea, 2002[31]	6	576	0.77	(0.54, 1.09)
Non-vertebral Shea, 2002[31]	2	222	0.86	(0.43, 1.72)
Clinical osteoporotic, all subjects Prince, 2006[95]	1	1,460	0.87	(0.67, 1.12)
Clinical osteoporotic, compliant subjects Prince, 2006[95]	1	830	0.66	(0.45, 0.97)

Estrogen

We identified four meta-analyses[21] and two publications from the Women's Health Initiative[101, 102] published after the meta-analysis that evaluated the effect of estrogen on fracture risk. The

meta-analyses[22, 25, 29] pooled data from 24 different RCTs. The RCTs included in these meta-analyses are detailed in Table 13.

Among three meta-analyses that evaluated risk for vertebral fracture, only one demonstrated a statistically significant risk reduction (Table 14). Risk estimates for non-vertebral and hip fractures were not statistically significant in any of the meta-analyses.

In the estrogen plus progestin component of the Women's Health Initiative, 16,608 postmenopausal women aged 50-79 years were randomized to received conjugated equine estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d, in one tablet or placebo. Estrogen plus medroxyprogesterone was associated with a 33% reduction in vertebral fracture, 33% reduction in hip fractures and 24% overall reduction in fracture compared to placebo, all of which were statistically significant.[101, 102] The hazards ratio for hip fracture was 0.66 (0.45-0.98).[102] The effects did not differ when stratified by age.

Table 13. Randomized controlled trials included in meta-analyses of effect of estrogen on fracture relative to placebo or no treatment.*

RCTs (Author, year)	Meta-analyses (Author, year)						
	Stevenson, 2005[29]				Torgerson, 2001[103]	Wells, 2002[104]	
	Fracture type†						
	V	NV	H	W	V	V	NV
Alexandersen, 1999[105]	X	X			X	X	X
Bjarnason, 2000[106]		X					
Cauley, 2001[107]			X	X			
Delmas, 2000[108]		X			X		
Eiken, 1997[109]		X					
Gallagher, 2001[110]	X	X			X		
Genant, 1997[111]		X					
Greenspan, 1998[112]						X	X
Herrington (HERS), 2000[113]		X	X	X	X		
Hosking, 1998[55]							X
Hully, 1998[114]						X	X
Ishida, 2001[115]					X		
Komulainen, 1997[116]							X
Lees, 2001[117]		X	X	X			
Lindsay, 1990[118]		X			X		
Lufkin, 1992[119]	X	X			X	X	
Mosekilde, 2000[120]	X	X			X		
Orr-Walker, 2000[121]		X					
PEPI, 1996[122]					X		
Ravn (EPIC), 1999[123]			X	X	X		
Recker, 1999[124]		X			X		
Rossouw (WHI), 2002[102]			X	X			
Wimalawamsa, 1998[69]		X			X	X	X
Weiss, 1999[125]		X					

*HERS= Heart and Estrogen/progestin Study, WHI = Women's Health Initiative; † V=vertebral, NV=nonvertebral, H=hip, W=wrist/forearm X= Included in pooled analysis.

Table 14. Pooled risk estimates of fracture for estrogen relative to placebo or no treatment among post-menopausal women.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Torgerson, 2001[103]	13	6,723	0.67	(0.45, 0.98)
Stevenson, 2005[29]				
Women with severe osteoporosis*	1	68	0.58	(0.26, 1.30)
Women with severe osteoporosis, osteoporosis or osteopenia	2	104	0.71	(0.24, 2.12)
Women not selected for low BMD	2	1,218	2.05	(0.71, 5.97)
Wells, 2002[104]	5	3,385	0.66	(0.41, 1.07)
Non-vertebral				
Stevenson, 2005[29]				
Women with severe osteoporosis	2	86	0.67	(0.12, 3.93)
Women with severe osteoporosis, osteoporosis or osteopenia	4	264	0.86	(0.37, 1.96)
Women with osteoporosis or osteopenia	1	128	1.17	(0.41, 3.28)
Women not selected for low BMD	13	7,316	0.86	(0.72, 1.02)
Wells, 2002[104]	6	5,383	0.87	(0.71, 1.08)
Hip				
Stevenson, 2005[29]				
Women not selected for low BMD	4	20,798	0.74	(0.53, 1.03)
Women's Health Initiative, 2003.[102]	1	16,608	0.66*	(0.45, 0.98).
Forearm/Wrist				
Stevenson, 2005[29]				
Women not selected for low BMD	4	4,160	0.95	(0.58, 1.53)

*Hazards ratio

1-34 parathyroid hormone

Teriparatide:

We identified one systematic review[29] that summarized data about the effect of teriparatide on fracture relative to placebo or no treatment among post-menopausal women. The RCTs included in this systematic review are detailed in Table 15. This systematic review reported risk estimates for vertebral, non-vertebral, hip, wrist, and humerus fractures (Table 16).

Table 15. Randomized controlled trials included in systematic review of the effect of teriparatide on fracture relative to placebo or no treatment.

RCTs (Author, year)	Systematic review (Author, year)				
	Stevenson, 2005[29]				
	Vertebral	Non-vertebral	Hip	Wrist	Humerus
Cosman, 2001[126]	X				
Neer, 2001[127]	X	X	X	X	X

Table 16. Pooled risk estimates of fracture for teriparatide relative to placebo or no treatment among post-menopausal women.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Stevenson, 2005[29]				
All subjects, dose 20 μg/d	1	892	0.35	(0.22, 0.55)
All subjects, dose 40 μg/d	1	882	0.31	(0.19, 0.50)
Subjects with severe osteoporosis	1	892	0.35	(0.22, 0.55)
Non-vertebral				
Stevenson, 2005[29]				
All subjects, dose 20 μg/d	1	1,085	0.65	(0.43, 0.98)
All subjects, dose 40 μg/d	1	1,096	0.60	(0.39, 0.91)
Subjects with severe osteoporosis	1	1,085	0.65	(0.43, 0.98)
Hip				
Stevenson, 2005[29]				
Subjects with severe osteoporosis	1	NR	0.50	(0.09, 2.73)
Wrist				
Stevenson, 2005[29]				
Subjects with severe osteoporosis	1	NR	0.54	(0.22, 1.35)
Humerus				
Stevenson, 2005[29]				
Subjects with severe osteoporosis	1	NR	0.80	(0.22, 2.98)

Selective Estrogen Receptor Modulators

Raloxifene:

We identified two meta-analyses[29, 30] that pooled data from two different RCTs to describe the effect of raloxifene on fracture risk reduction relative to placebo or no treatment among post-menopausal women. The RCTs included in these meta-analyses are detailed in Table 17. These meta-analyses reported risk estimates for vertebral, non-vertebral, hip and wrist fractures (Table 18).

Table 17. Randomized controlled trials included in meta-analyses of effect of raloxifene on fracture relative to placebo or no treatment.

RCTs (Author, year)	Meta-analyses (Author, year)					
	Schachter, 2005[30]		Stevenson, 2005[29]			
	Vertebral	Non-vertebral	Vertebral	Non-vertebral	Hip	Wrist
Ettinger, 1999[128]	X		*	*	*	*
Lufkin, 1998[129]	X		*	*	*	

X= Included in pooled analysis; * identified but not included in pooled analysis.

Table 18. Risk estimates of fracture for raloxifene relative to placebo or no treatment among post-menopausal women.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Schachter, 2005[30]				
Ettinger study at four years	1	7,705	0.60	(0.52, 0.69)
Ettinger and Lufkin studies at four years	2	7,848	0.81	(0.43, 1.51)
Stevenson, 2005[29]				
Women with severe osteoporosis	1	NR	0.69	(0.56, 0.86)
Women with severe osteoporosis or osteoporosis	1	4,551	0.65	(0.53, 0.79)
Women with osteoporosis	1	NR	0.53	(0.35, 0.79)
Women with osteopenia	1	NR	0.53	(0.32, 0.88)
Non-vertebral				
Stevenson, 2005[29]				
Women with severe osteoporosis or osteoporosis	1	6,828	0.92	(0.79, 1.07)
Hip				
Stevenson, 2005[29]				
Women with severe osteoporosis or osteoporosis	1	6,828	1.12	(0.65, 1.95)
Wrist				
Stevenson, 2005[29]				
Women with severe osteoporosis or osteoporosis	1	6,828	0.89	(0.68, 1.15)

Tamoxifen:

We did not identify any studies that evaluated the risk of fracture with tamoxifen relative to placebo.

Testosterone

We did not identify any studies that evaluated the risk of fracture with testosterone relative to placebo.

Vitamin D

We identified 4 meta-analyses[29, 33-35] that pooled data from 28 different RCTs to describe the effect of vitamin D on fracture risk reduction relative to placebo or no treatment. The populations included in these meta-analyses were: men or women with osteoporosis,[34] older adults[35] and postmenopausal women[33, 130] The RCTs included in these meta-analyses are detailed in Table 19. These meta-analyses reported risk estimates for vertebral, non-vertebral and hip fractures (Table 20).

The first meta-analysis,[34] which included RCTs and quasi-randomized trials of vitamin D and its analogues, found that vitamin D alone had no statistically significant effect on hip, vertebral, or any new fracture. Vitamin D with calcium marginally reduced hip fractures (RR 0.81, 95% C.I. 0.68-0.96) but did not have any effect on vertebral fractures. The effect appeared to be restricted to those living in institutional care.

The next meta-analysis evaluated the efficacy of vitamin D treatment in preventing postmenopausal osteoporosis and included 25 RCT of standard or hydroxylated vitamin D with or without calcium supplementation or a control that were published between 1966 and 1999.[33] Vitamin D reduced the risk of vertebral fractures (RR=0.63, 95% C.I. 0.45-0.88). A non-significant trend was seen for nonvertebral fractures (RR=0.77, p=0.09). The authors acknowledge that inferences from these analyses are limited by variability in design, difference in vitamin D formulation, differences in populations studied, and inconsistent outcome measures.

The third meta-analysis, evaluated fracture prevention with vitamin D supplementation and did include studies with men.[35] Five RCT with hip fracture as an outcome and 7 RCT with nonvertebral fracture as an outcome were included. All trials used standard vitamin D3 (cholecalciferol). A vitamin D dose of 700 to 800 I.U. daily was associated with a reduced risk of hip fracture (RR=0.74, 95% C.I. 0.61-0.88) and a reduced risk of any nonvertebral fracture (RR=0.77, 95% C.I. 0.68-0.8). Doses of 400 I.U. daily were not effective in preventing hip and nonvertebral fractures.

The last of these meta-analyses[29] evaluated the effect of vitamin D on fractures in postmenopausal women. This meta-analyses stratified based on whether subjects had osteopososis at study enrollment or were not selected based on BMD. In this meta-analysis vitamin-D had no effect on fracture in either strata.

Table 19. Randomized controlled trials included in meta-analyses of effect of vitamin D on fracture relative to placebo or no treatment.

RCTs (Author, year)	Meta-analyses (Author, year)								
	Avenell, 2005[34]			Bischoff-Ferrari, 2005[35]		Papadimitropoulos 2002[33]		Stevenson, 2005[29]	
	V	NV	H	NV	H	V	NV	V	NV
Aloia, 1988[131]								X	
Avenell, 2004[132]	X		X						
Baeksgaard, 1998[133]						X			
Cannigia, 1984[134]						X		X	
Chapuy, 1994[135]				X	X				
Chapuy, 1992[135]							X		
Chapuy, 2002[136]				X	X				
Dawson-Hughes, 1997[137]				X	X		X		
Dukas, 2004[138]		X							
Gallagher, 2001[110]			X			X			X
Gorai,1999[139]		X							
Grant, 2005[140]	X								
Guesens, 1986[141]						X			
Harwood, 2004[142]			X						
Lipps, 1996[143]			X	X	X		X		
Meyer, 2002[144]			X	X	X				
Oriomo, 1987[145]						X			
Oriomo, 1994[146]						X	X		
Ott, 1989[147]						X	X	X	X
Peacock, 2000[148]	X								
Pfeifer, 2000[149]				X	X				
Sato, 1997[150]			X						
Sato, 1999a[151]		X	X						
Sato, 1999b[152]			X						
Smith, 2004[153]			X						
Tilyard, 1992[154]						X	X		
Trivedi, 2003[155]	X		X	X	X				
Ushirooyama, 2001[156]		X							

X= Included in pooled analysis; * identified but not included in pooled analysis

Table 20. Risk estimates of fracture for vitamin D relative to placebo or no treatment.

Type of fracture	# studies	Sample size	RR	(95% CI)
Vertebral fractures				
Avenell, 2005[34]				
Standard vitamin-D [D2, D3, or 25(OH)D]				
Not selected on basis of prior osteoporotic fracture	2	2,953	0.96	(0.42, 2.21)
Selected on basis of prior osteoporotic fracture	1	2745	3.97	(0.44, 35.45)
Either selected or not selected on basis of prior osteoporotic fracture	3	5698	1.13	(0.50, 2.55)
Papadimitropoulos, 2002[33]				
Standard vitamin-D [D2, D3, or 25(OH)D]	1	160	0.33	(0.01, 8.05)
Calcitriol (1,25-OH vitamin D)	7	970	0.64	(0.44, 0.92)
Either Standard vitamin-D or Calcitriol	8	1130	0.63	(0.45, 0.88)
Stevenson, 2005[29]				
Women with severe osteoporosis	3	109	1.02	(0.44, 2.32)
Elderly women not selected for BMD	1	NR	4.44	(0.50, 39.03)
Non-vertebral				
Avenell, 2005[34]				
Alphacalciferol				
Not selected on basis of prior osteoporotic fracture	2	466	0.40	(0.05, 3.08)
Bischoff-Ferrari, 2005[35]				
All doses	7	9820	0.83	(0.70, 0.98)
700-800IU/d	5	6098	0.77	(0.68, 0.87)
400IU/d	2	3722	1.03	(0.86, 1.24)
Stevenson, 2005[29]				
Women with severe osteoporosis or osteoporosis	1	86	2.50	(0.51, 12.19)
Elderly women not selected for BMD	1	213	0.46	(0.17, 1.27)
Papadimitropoulos, 2002[33]				
Standard vitamin-D [D2, D3, or 25(OH)D]	3	5399	0.78	(0.55, 1.09)
Calcitriol (1,25-OH vitamin D)	3	788	0.87	(0.29, 2.59)
Either Standard vitamin-D or Calcitriol	6	6187	0.77	(0.57, 1.04)
Hip				
Avenell, 2005[34]				
Standard vitamin-D [D2, D3, or 25(OH)D]				
Not selected on basis of prior osteoporotic fracture	4	15948	1.20	(0.98, 1.47)
Selected on basis of prior osteoporotic fracture	3	2820	1.08	(0.72, 1.62)
Either selected or not selected on basis of prior osteoporotic fracture	7	18668	1.17	(0.98, 1.41)

Type of fracture	# studies	Sample size	RR	(95% CI)
Alphacalciferol				
Not selected on basis of prior osteoporotic fracture	3	239	0.16	(0.04, 0.69)
Calcitriol (1,25-OH vitamin D)				
Not selected on basis of prior osteoporotic fracture	1	246	0.33	(0.01, 8.10)
Bischoff-Ferrari, 2005[35]				
All doses	5	9294	0.88	(0.69, 1.13)
700-800IU/d	3	5572	0.74	(0.61, 0.88)
400IU/d	2	3722	1.15	(0.88, 1.50)

*Based on single study.

Within Class Comparisons

Bisphosphonates

We identified eight RCTs[46, 157-164] that included head-to-head comparisons of three different bisphosphonates pairs (Table 21). For the most part, these studies were not designed or powered to compare fracture outcomes but rather to compare changes in intermediate outcomes such as bone mineral density and changes in markers of bone turnover. Only one[157] of the head-to-head trials was designed to compare facture outcomes; this study was designed to compare risedronate to etidronate for the prevention of vertebral fractures.

Table 21. Head to head trials of bisphosphonates with fracture outcomes.

	Alendronate	Etidronate	Ibandronate	Pamidronate	Residronate	Zolendronic acid
Alendronate	**********					
Etidronate	3	**********				
Ibandronate	0	0	**********			
Pamidronate	0	0	0	**********		
Residronate	3	2	0	0	**********	
Zolendronic acid	0	0	0	0	0	**********

Alendronate *vs.* Etidronate:

We identified 3 RCTs[159, 160, 164] that compared fracture risk between treatment with alendronate and etidronate. Fracture was a secondary outcome in each of these studies and none were powered to detect differences in fracture across groups. The study populations were post-menopausal women with osteoporosis,[164] women with osteoporosis[160] and osteopenic women with primary billiary cirrhosis.[159] Two studies compared alendronate alone to etidronate alone.[159, 160] Both studies were small and neither demonstrated any difference in fracture risk between alendronate and etidronate (Table 22).

Table 22. Fractures with alendronate relative to etidronate, by fracture type.

Author, year	Type of fracture	Number of fractures, alendronate	Number of fractures, etidronate	Odds ratio (95% CI)
Guanabens, 2003[159]	non-vertebral	2/130	1/13	2.06 (0.19, 21.85)
Guanabens, 2003[159]	vertebral	0/13	0/13	
Iwamoto, 2003[160]	vertebral	0/25	1/25	0.14 (0.00, 6.82)

One RCT[164] compared the efficacy of etidronate alone and alendronate/etidronate combination therapy in the prevention of fractures. No vertebral or non-vertebral fractures were observed in either study arm. However, fractures were a secondary outcome and the study did not have power to detect differences between groups (20 subjects in each treatment group).

Alendronate *vs.* Risedronate:

We identified 3 RCTs[161-163] that compared fracture risk between treatment with alendronate and risedronate. Fractures were a secondary outcome in one of these studies[163] and collected as adverse events in the other two;[161, 162] none were powered to detect differences in fracture across groups. All studies were restricted to women with osteoporosis or osteopenia. Two of the studies specified that the women were post-menopausal.[161, 162] Across all doses and all type of fractures that were assessed, there were no differences in fracture risk between alendronate and risedronate (Table 23).

Table 23. Fractures with alendronate relative to risedronate, by fracture type among women with osteoporosis.*

Author, year	Study duration	Type of fracture	Number of fractures, alendronate	Number of fractures, risedronate	Odds ratio (95% CI)
Muscoso, 2004[163]	12 months	femoral	1/1000	0/100	NC
Muscoso, 2004[163]	24 months	femoral	2/1000	0/100	NC
Rosen, 2005[162]	12 months	fracture	26/520	20/533	1.35 (0.75, 2.43)
Hosking, 2003[161]	12 months	fracture, clinical	6/172	6/178	1.04 (0.33, 3.27)
Muscoso, 2004[163]	12 months	radial	1/1000	0/100	NC
Muscoso, 2004[163]	24 months	radial	0/1000	0/100	NC
Muscoso, 2004[163]	12 months	vertebral	2/1000	0/100	NC
Muscoso, 2004[163]	24 months	vertebral	4/1000	0/100	NC

*NC = not calculable

Etidronate *vs.* Risedronate:

We identified two RCTs[157, 158] that compared fracture risk between treatment with etidronate and risedronate. In one study,[157] incidence of new vertebral fractures was the primary outcome; this study had sufficient sample size to demonstrate noninferiority of risedronate to etidronate for the prevention of vertebral fractures. Fracture incidence was a secondary outcome in the other study[158] and it did not have power to detect fracture incidence across groups. The inclusion criteria for one study was post-menopausal women with osteoporosis,[157] the other men or women with osteoporosis, although only 1% of the sample was male.[158] Neither study demonstrated any difference in fracture risk between etidronate and risedronate (Table 24).

Table 24. Fractures with etidronate relative to risedronate, by fracture type.

Author, year	Type of fracture	Number of fractures, etidronate	Number of fractures, risedronate	Odds ratio (95% CI)
Fukunaga, 2002[158]	non-vertebral	4/117	7/118	0.57 (0.17, 1.91)
Fukunaga, 2002[158]	vertebral	2/111	0/101	6.81 (0.42, 1.10)
Kushida, 2004[157]	vertebral	13/217	19/216	0.66 (0.32, 1.36)

Selective Estrogen Receptor Modulators

We did not identify any head to head trials between SERMs that assessed effect on fractures.

Between Class Comparisons

We identified 17 RCTs[55, 69, 126, 163-176] that included head-to-head comparisons of 11 different drug pairs (Table 25).

Table 25. Head to head trials between classes of agents used to treat or prevent osteoporosis that with fracture outcomes.

	BIsphosphonate	Calcitonin	Calcium	Estrogen	PTH	SERMS	Testosterone	Vitamin D	Exercise
BIsphosphonate	**********								
Calcitonin	2	**********							
Calcium	2	0	**********						
Estrogen	7	1	0	**********					
PTH	2	1	0	2	*********				
SERMS	2	0	0	1	0	**********			
Testosterone	0	0	0	0	0	0	**********		
Vitamin D	2	2	0	0	0	0	0	*********	
Exercise	0	0	0	0	0	0	0	0	*********

Bisphosphonate *vs.* Calcitonin:

We identified two studies[169, 172] that compared the effects of a bisphosphonate and calcitonin on fracture incidence. Fractures were secondary outcomes in each and neither was powered to detect differences in fracture rate across arms. In one study the population was postmenopausal women with osteoporosis;[169] in the other, organ transplant recipients that were primarily male.[172] The bisphosphonate in both studies was etidronate. Both studies were small and no difference in fracture incidence between etidronate and calcitonin was found in either (Table 26).

Table 26. Fractures with etidronate relative to calcitonin, by fracture type.

Author, year	Type of fracture	Number of fractures, etidronate	Number of fractures, calcitonin	Odds ratio (95% CI)
Ishida, 2004[169]	vertebral	8/66	8/66	1.00 (0. 35, 2.83)
Garcia-Delgado, 1997[172]	vertebral	3/14	4/13	0.31 (0. 12, 3.39)

Bisphosphonate *vs.* Estrogen:

We identified seven studies[55, 69, 165, 166, 169, 171, 173] that compared the effects of a bisphosphonate (with or without estrogen) compared to estrogen (with or without bisphosphonates) among post-menopausal women. There were five studies that compared a bisphosphonate alone to estrogen,[55, 69, 165, 169, 171] three that compared a bisphosphonate plus estrogen to estrogen,[69, 165, 171] and five that compared a bisphosphonate plus estrogen to a bisphosphonate alone.[69, 165, 166, 171, 173] Data on fracture incidence was collected as either adverse events or as a secondary outcome in all of these studies. None of the studies were powered to detect differences in fracture incidence across study arms.

Bisphosphonate vs. estrogen

Among the five studies that compared a bisphosphonate alone to estrogen, three compared alendronate and estrogen;[55, 165, 171] two compared etidronate and estrogen.[69, 169] There was no difference in fracture incidence between either of the bisphosphonates and estrogen (Table 27). Fracture data were collected as adverse events in the three studies that compared alendronate and estrogen;[55, 165, 171] they were collected as secondary endpoints in the studies that compared etidronate and estrogen.[69, 169] None of the studies were powered to detect differences in fracture rates across study arms.

Table 27. Fractures with bisphosphonate relative to estrogen, among postmenopausal women.

Author, year	Fracture type	Number of fractures, bisphosphonate	Number of fractures, estrogen	Odds ratio (95% CI)
		Alendronate		
Hosking, 1998[55]	non-vertebral	44/897	6/204	1.58 (0. 56, 4.43)
Bone, 2000[165]	clinical fracture	5/92	10/143	0.77 (0. 26, 2.25)
Greenspan, 2003[171]	clinical fracture	7/93	5/93	1.43 (0. 44, 4.58)
		Etidronate		
Ishida, 2004[169]	vertebral	8/66	7/66	1.16 (0. 40, 3.39)
Wimalawansa, 1998[69]	non-vertebral	1/14	1/15	1.07 (0. 06, 18.10)
Wimalawansa, 1998[69]	vertebral	3/14	2/15	1.73 (0. 26, 11.50)

Bisphosphonate plus estrogen vs. bisphosphonate

Among the three studies that compared a bisphosphonate plus estrogen to a bisphosphonate, two compared alendronate plus estrogen to alendronate alone[165, 171] and one compared etidronate plus estrogen to etidronate alone.[177] There was no difference in fracture incidence between either of the bisphosphonate-estrogen combinations and the bisphosphonate alone (Table 28). Fracture data were collected as adverse events in the studies that compared alendronate and estrogen;[55, 165, 171] they were collected as secondary endpoints in the study that compared etidronate and estrogen.[69, 169] None of the studies were powered to detect differences in fracture rates across study arms.

Table 28. Fractures with bisphosphonate plus estrogen relative to bisphosphonate alone, among postmenopausal women.

Author, year	Fracture type	Number of fractures, bisphosphonate	Number of fractures, estrogen	Odds ratio (95% CI)
		Alendronate		
Bone, 2000[165]	clinical fracture	8/140	5/92	1.05 (0. 34, 3.30)
Greenspan, 2003[171]	clinical fracture	4/94	7/93	0.56 (0. 16, 1.87)
		Etidronate		
Wimalawansa, 1998[69]	non-vertebral	1/15	1/14	0.93 (0. 06, 15.69)
Wimalawansa, 1998[69]	vertebral	1/15	3/14	0.30 (0. 04, 2.40)

Bisphosphonate plus estrogen vs. estrogen

Among the five studies that compared a bisphosphonate in combination with estrogen to estrogen alone, three compared alendronate plus estrogen to estrogen alone;[165, 171, 173] one compared etidronate plus estrogen to estrogen alone,[171] and one compared risedronate plus estrogen to estrogen alone.[166] There was no difference in fracture incidence between any of the bisphosphonate-estrogen combinations and estrogen alone (Table 29). Fracture data were collected as adverse events in all but one of the studies,[166] in which fractures were a secondary outcome. None of the studies were powered to detect differences in fracture rates across study arms.

Table 29. Fractures with bisphosphonate plus estrogen, relative to estrogen alone, among post-menopausal women.*

Author, year	Fracture type	Number of fractures, bisphosphonate plus estrogen	Number of fractures, estrogen	Odds ratio (95% CI)
		Alendronate		
Bone, 2000[165]	non-vertebral	8/140	10/143	0.81 (0. 31, 2.09)
Greenspan, 2003[171]	clinical fracture	4/94	5/93	0.78 (0. 21, 2.98)
Lindsay, 1999[173]	clinical fracture	15/203	9/191	1.59 (0. 70, 3.64)
Lindsay, 1999[173]	clinical fracture	0/203	0/191	NC
		Etidronate		
Greenspan, 2003[171]	clinical fracture	1/15	1/15	1.00 (0. 06, 16.79)
		Risedronate		
Harris, 2001[166]	non-vertebral	2/168	7/155	0.29 (0. 08, 1.11)
Harris, 2001[166]	vertebral	3/168	4/155	0.69 (0. 15, 3.07)

*NC=not calculable

Bisphosphonate *vs.* PTH:

We identified two studies[168, 175] that compared the effects of a bisphosphonate and PTH (daily or cyclical administration) on fracture incidence among post-menopausal women. The bisphosphonate in both studies was alendronate. In one study,[168] the likelihood of non-vertebral fracture was higher with alendronate than with PTH (OR 3.24, 95% CI 1.04-10.07). However,

there was no difference between alendronate and PTH in the likelihood of non-vertebral in the other study (Table 30).[175] Fractures were secondary outcomes in each of these studies; neither were powered to detect differences in fracture rates across arms.

Table 30. Fractures with alendronate relative to PTH, by PTH dosing regimen, among post-menopausal women.

Author, year	Fracture type	Number of fractures, Alendronate	Number of fractures, PTH	Odds ratio (95% CI)
		Daily PTH		
Body, 2002[168]	non-vertebral	10/73	3/73	3.24 (1.04, 10.07)
Cosman, 2005[175]	non-vertebral	4/38	2/36	1.93 (0.37, 10.14)
Cosman, 2005[175]	vertebral	1/38	4/36	0.27 (0.04 ,1.61)
		Cyclical PTH		
Cosman, 2005[175]	non-vertebral	2/34	2/36	1.06 (0.14, 7.88)
Cosman, 2005[175]	vertebral	2/34	4/36	0.52 (0.10, 2.73)

Bisphosphonate *vs.* SERMS:

We identified two studies[163, 170] that compared the effects of a bisphosphonate and a SERM on fracture incidence among women with osteoporosis among women with osteoporosis. Although only one of the studies specified osteoporosis as an inclusion criterion[170] the average age of the women enrolled in the other study was 68 years.[163] The SERM in both studies was raloxefine. Alendronate was compared to raloxefine both studies. Risedronate was compared to raloxefine in one study.[163] There was no difference in fracture incidence between either of the bisphosphonates and raloxefine (Table 31). Data on fractures were collected as adverse events in one of the studies[178] and as secondary outcomes in the other.[163] Neither study was powered to detect differences in fracture rates across study arms.

Table 31. Fractures with bisphosphonates relative to raloxefine.

Author, year	Fracture type	Number of fractures, bisphosphonate	Number of fractures, raloxefine	Odds ratio (95% CI)
		Alendronate		
Luckey, 2004[170]	all clinical fractures	5/221	8/230	0.65 (0.22, 1.95)
Muscoso, 2004[163]	femoral	1/1000	0/100	NC
Muscoso, 2004[163]	radial	1/1000	0/100	NC
Muscoso, 2004[163]	vertebral	2/1000	0/100	NC
		Residronate		
Muscoso, 2004[163]	femoral	0/100	0/100	NC
Muscoso, 2004[163]	radial	0/100	0/100	NC
Muscoso, 2004[163]	vertebral	0/100	0/100	NC

Bisphosphonate *vs.* Vitamin D:

We identified two studies[169, 172] that compared the effects of a bisphosphonate and a vitamin D preparation on fracture incidence. In one study the population was comprised of postmenopausal women with osteoporosis;[169] in the other of organ transplant recipients that were primarily male.[172] The bisphosphonate in both studies was etidronate. Etidronate was compared to alfacalcidol in one study[169] and to calcidiol[172] in the other. There was no difference in fracture incidence between etidronate and either of the vitamin D preparations (Table 32). Data on fractures were collected as secondary outcomes in both studies; neither was powered to detect differences in fracture rates across study arms.

Table 32. Fractures with etidronate relative to vitamin D, by vitamin D preparation.

Author, year	Fracture type	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
		Alfacalcidol		
Ishida, 2004[169]	vertebral	8/66	1/66	0.69 (0.26 1.83)
		Calcidiol		
Garcia-Delgado, 1997[172]	vertebral	3/14	0/13	8.08 (0.76 85.33)

Calcitonin *vs.* Estrogen:

We identified one study[169] that compared the effect of calcitonin and estrogen on fracture incidence among postmenopausal women. There was no difference in fracture incidence between calcitonin and estrogen (Table 33). Fracture incidence was a secondary outcome in this study and it was not powered to detect differences in fracture rates across study arms.

Table 33. Fractures with calcitonin relative to estrogen among postmenopausal women.

Author, year	Fracture type	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
Ishida, 2004[169]	vertebral	8/66	7/66	1.16 (0.40, 3.39)

Calcitonin *vs.* PTH:

We identified one study[174] that compared the effects of calcitonin and PTH. In this study the combination of calcitonin plus PTH was compared to PTH alone among postmenopausal women with osteoporosis. There was no difference in fracture incidence between these groups (Table 34). Fracture incidence was a secondary outcome in this study and it was not powered to detect differences in fracture rates across study arms.

Table 34. Fractures with calcitonin plus PTH, relative to PTH alone, among postmenopausal women with osteoporosis.

Author, year	Fracture type	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
Hodsman, 1997[174]	non-vertebral	0/13	0/11	NC
Hodsman, 1997[174]	vertebral	4/13	1/11	3.52 (0.51, 24.41)

Calcitonin *vs.* Vitamin D:

We identified two studies[169, 172] that compared the effects of calcitonin and vitamin D on fracture incidence. In one study the population was comprised of postmenopausal women with osteoporosis;[169] in the other of organ transplant recipients that were primarily male.[172] One study demonstrated in increased risk of vertebral fracture with calcitonin relative to vitamin D. Although the result was statistically significant, the confidence interval was very wide and the sample size was small. In the other study there was no difference in fracture incidence between these groups (Table 35). Fracture incidence was a secondary outcome in each study; neither was powered to detect differences in fracture rates across study arms.

Table 35. Fractures with calcitonin relative to vitamin D.

Author, year	Fracture type	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
Ishida, 2004[169]	vertebral	8/66	11/66	0.69 (0.26, 1.83)
Garcia-Delgado, 1997[172]	vertebral	4/13	0/13	9.71 (1.20, 78.42)

Estrogen *vs.* PTH

We identified two studies[126, 172] that compared the effects of estrogen and PTH on fracture incidence among post-menopausal women with osteoporosis (Table 36). In one study the risk of developing a vertebral fracture was lower with calcitonin relative to vitamin D. There was no difference vertebral fracture risk between these agents in another study.[167] Data on fractures were collected as secondary outcomes in both studies. Neither study was powered to detect differences in fracture rates across study arms.

Table 36. Fractures with estrogen, relative to PTH, among post-menopausal women with osteoporosis.

Author, year	Fracture type	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
Cosman, 2001[126]	non-vertebral	0/27	1/25	0.12 (0.00, 6.31)
Cosman, 2001[126]	vertebral	2/27	12/25	0.13 (0.04 ,0.45)
Lindsay, 1997[167]	vertebral	2/13	7/17	0.31 (1.06 ,1.44)

SERM *vs.* Estrogen

We identified one study[176] that compared the effects of raloxefine and estrogen on fracture incidence among post-menopausal women. There was no difference in fracture incidence between these groups (Table 37). Data on fracture incidence were collected as adverse events. This study was not powered to detect differences in fracture rates between study arms.

Table 37. Fractures with raloxefine, relative to estrogen, among post-menopausal women.

Author, year	Fracture type	Number of fractures, etidronate	Number of fractures, vitamin D	Odds ratio (95% CI)
Reid, 2004[176]	vertebral	1/102	1/102	1.00 (0.06, 16.10)
Reid, 2004[176]	vertebral	3/91	1/102	3.11 (0.43 ,22.51)

Key Question 2. How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment), age, gender, glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized; vitamin D deficient vs. not)?

Key Points

- The population in the majority of studies was post-menopausal women with osteopenia or osteoporosis.
- There is good evidence from RCTs that, compared with placebo, the bisphosphonates, calcitonin, PTH, and raloxefine prevent vertebral fractures among post-menopausal women.
- There is evidence from one RCT that, compared with placebo, PTH prevents non-vertebral fractures among post-menopausal women.
- There is good evidence from RCTs that, compared with placebo, risedronate prevents hip fractures among post-menopausal women.
- There are limited and inconclusive data on the effect of agents for the prevention and treatment of osteoporosis on transplant recipients and chronic patients treated with corticosteroids.

Detailed Analyses

Among the fifteen meta-analyses reviewed for this report, five performed analyses that evaluated the effect of therapy for different groupings of disease severity (Table 38); four stratified based specifically on severity of bone loss;[21, 25, 29, 34] two stratified based on whether therapy was given for prevention or treatment.[21, 23] In some instances, pooled estimate for fracture risk of the population with more severe osteopenia or osteoporosis reached statistical significance when pooled estimate of the population with less severe osteoporosis or osteopenia did not. Similarly, in some instances, pooled estimate for fracture risk of the population with more severe osteopenia or osteoporosis reached a higher point estimate than did the estimate for the population with less severe osteoporosis or osteopenia. However, in all instances the point estimates for the more severe populations fell within the 95% confidence intervals for the estimates of the less severe population.

Table 38. Risk of developing fracture for populations with more severe osteoporosis or osteopenia compared to populations with less severe osteoporosis or osteopenia, by drug.

	Degree of osteopenia or osteoporosis	
	Less severe	More severe
Alendronate		
Cranney, 2002[21]		
Prevention *vs.* treatment trials	0.45*†	0.52
	(0.06, 3.15)	(0.43, 0.65)
Stevenson, 2005[29]		
	0.53‡†	0.60
	(0.42, 0.67)	(0.46, 0.80)
Cranney, 2002[21]	0.51§‖	0.51
	(0.38, 0.69)	(0.38, 0.69)
Stevenson, 2005[29]	0.74‡‖	0.81
	(0.52, 1.06)	(0.66, 0.98)
Papapoulos, 2004[25]	0.56¶**	0.45
	(0.36, 0.84)	(0.28, 0.71)
Stevenson, 2005[29]	0.68‡**	0.46
	(0.30, 1.54)	(0.23, 0.91)
Stevenson, 2005[29]	0.67‡††	0.48
	(0.19, 2.32)	(0.31, 0.75)
Etidronate		
Cranney, 2001[23]	0.61*†	0.59
	(0.29, 1.26)	(0.38, 0.94)
Cranney, 2001[23]	1.05*‖	0.75
	(0.69, 1.60)	(0.34, 1.70)
Risedronate		
Stevenson, 2005[29]	0.60‡‡**	0.66
	(0.42, 0.88)	(0.48, 0.89)
Estrogen		
Stevenson, 2005[29]	0.71§§†	0.58
	(0.24, 2.12)	(0.26, 1.30)
Stevenson, 2005[29]	1.17¶¶‖	0.67
	(0.41, 3.28)	(0.12, 3.93)

Table 38. (continued) Risk of developing fracture for populations with more severe osteoporosis or osteopenia compared to populations with less severe osteoporosis or osteopenia, by drug.

	Degree of osteopenia or osteoporosis	
	Less severe	More severe
Raloxefine		
Stevenson, 2005[29]	0.53¶¶†	0.69
	(0.35, 0.79)	(0.56, 0.86)
Vitamin D		
Avenell, 2005[34]	0.96‖ ‖†	3.97
	(0.42, 2.21)	(0.44, 35.45)
Avenell, 2005[34]	1.20‖ ‖**	1.08
	(0.98, 1.47)	(0.72, 1.62)

* prevention trial vs. treatment trial, †vertebral fracture, ‡ osteoporosis or osteopenia vs. osteoporosis, § treatment trials vs. all trials, ‖ non-vertebral fracture, ¶ T score ≤ 2.0 or with vertebral fracture vs. T score ≤ 2.5 or with vertebral fracture, ** hip fracture, †† forearm or wrist fracture, ‡‡ established osteoporosis vs. severe osteoporosis, §§ severe osteoporosis, osteoporosis or osteopenia vs. severe osteoporosis, ¶¶osteoporosis or osteopenia vs. severe osteoporosis, ‖ ‖ selected based on prior osteoporotic fracture vs. not selected based on prior osteoporotic fracture.

No direct comparisons were made between subpopulations in any of the RCTs reviewed for this report. Among the RCTs reviewedfor this report, the study population was comprised of post-menopausal women with osteopenia or osteoporosis in most.

Eight trials were performed in special populations with increased risk for osteoporosis: six were performed among recipients of solid organ transplants,[41, 43, 44, 46, 172, 179] one among patients undergoing chemotherapy for lymphoma,[39] and one among women with primary biliary cirrhosis.[159] Among these studies, five assessed the effect of pamidronate on fracture incidence relative to placebo or control. The pooled estimate of fracture risk for pamidronate relative to placebo is 0.51 (95% CI, 0.21-1.24). One study found no association between ibandronate and fracture risk relative to placebo among renal transplant recipients.[40] The relative risk of fracture did not differ between etidronate and calcitonin[172] or alendronate and etidronate[159] among patient who had undergone transplant or who had primary biliary cirrhosis, respectively.

Glucocorticoid-induced osteoporosis

We identified one systematic review[180] and three studies published subsequent to the review[181-183] that evaluated effect of bisphosphonates on fracture incidence among subjects treated with glucocorticoids. The systematic review identified nine studies[178, 184-191] published before 1999 that reported fracture data, although not as the primary outcome (Table 39). The authors of the systematic review report that six of the studies[178, 184-187, 190] analyzed the difference between treatment and control group with regard to fracture risk; three found a trend in reduced fracture rate[178, 184, 186] and one demonstrated a 10.1% reduction in vertebral fractures among patients treated with risedronate compared to control.[178] Among the studies published after the systematic review, one[183] that compared risedronate and placebo demonstrated a statistically

significant reduction in the absolute risk and relative risk of incident radiographic vertebral fractures (11% and 70%, respectively) after one year. Another,[182] which compared alendronate and placebo, demonstrated a significant reduction in the risk of incident radiographic vertebral fractures (0.7% with alendronate versus 6.8% with placebo; $p < 0.05$). The third trial[181] compared two different daily doses of risedronate with placebo. A significant reduction in the incidence of vertebral fractures of 70% was found for the combined risedronate groups, although the trial was not powered to show fracture efficacy.

Table 39. RCTs of bisphosphonates used to treat or prevent glucocorticoid-induced osteoporosis that report fracture data.

Author; year	Bisphosphonate	Control	N	Mean daily steroid dose	Population	Results
Studies included in systematic review						
Adachi et al., 1997[184]	Cyclical etidronate: 400 mg/d X 2weeks, then 500 mg/d Ca X 11 weeks; could use 1000 u/d vit D	Cyclical placebo, then 500 mg/d Ca; could use 1000 u/d vitamin D	117	11 mg prednisone	Primary; 42 men/75 women Mean age 58 years with primarily RA, PMR	24% baseline osteoporotic
Cohen, 1999[178]	Risedronate 2.5 or 5 mg/d + 1000mg/d Ca + 400 u/d vit D	Placebo + 1000 mg/d Ca + 400u/d vit D	290	15 mg prednisone	Secondary, men and women Mean age 58.4, primarily RA, PMR	34% baseline vertebral fracture
Cortet, 1999[191]	Cyclical etidronate 400 mg/d X 2 weeks then 500 mg/d Ca X 11 weeks	500 mg/d Ca	12	nr	Primary, 3 men/ 9 women (33% postmenopausal) with primary biliary cirrhosis	100% normal Z scores (azathioprine also used)
Geusens, 1998[190]	Cyclical etidronate 400 mg/d X 2 weeks then 500 mg/d Ca X 11 weeks; could use 1000 u/d vit D	Cyclical placebo, then 500 mg/d Ca; could use 1000 u/d vitamin D	83	12.5 mg prednisone	Primary, 28 men/ 55 women (84% postmenopausal) with primary RA and PMR	100% osteopenic
Jenkins, 1999[189]	Cyclical etidronate 400 mg/d X 2 weeks then 97 mg/d Ca + 400 u/d vit D X 11 weeks	Cyclical placebo then 97 mg/d Ca + 400400 u/d vit D	49	7.5 mg prednisolone	Secondary 19 men/ 30 women, mean age 59 years, with asthma, PMR, and SLE	100% baseline osteopenic (2 years)
Jensen, 1998[187]	400 mg/d etidronate X 2 weeks out of 15 + 1000 mg/d Ca	1000 mg/d Ca	55	8.5 mg prednisone	Unknown combination 11 men/ 44 women (mean age 64) with primarily PMR, TA, asthma	83% of reported baseline fracture (2 years)
Roux, 1998[185]	Clodronate 800, 1600, or 2400 mg/d	Placebo	74	8 mg prednisolone	Secondary 33 men/ 41 women (73% postmenopausal) age range 39-73, with asthma or COPD	68% baseline osteopenic; 29.5% baseline osteoporotic

Table 39. (continued) RCTs of bisphosphonates used to treat or prevent glucocorticoid-induced osteoporosis that report fracture data.

Author; year	Bisphosphonate	Control	N	Mean daily steroid dose	Population	Results
Studies included in systematic review						
Saag, 1998[186]	Risedronate 2.5, 5, or 10 mg/d + 500 mg/d Ca	Placebo + 500 mg/d Ca	477	21 mg prednisone	Primary 477 men and women (70% postmenopausal) mean age 59.4±14.3, primarily RA, PMR, SLE	30% baseline vertebral fracture
Skingle, 1999[188]	Cyclical etidronate 400 mg/d X 2 wks then 500 mg/d Ca 11 wks	Cyclical placebo then 500 mg/d Ca	28	9 mg/d prednisolone	Primary 11 men/ 17 women with PMR or RA	
Studies published after systematic review						
Adachi, 2001[182]	Alendronate 5 or 10 mg X 24 mos (or 2.5 mg for 12 mos and 10 mg for 12 mos) + 800-1000 mg/d Ca + 250-500 u/d vit D	Placebo + 800-1000 mg/d Ca + 250-500 u/d vit D	208	7.5 mg prednisone (10 mg in year 2)	66 men/ 142 women (63% postmenopausal) , age range 21-79	90% reduction in vertebral fractures (2 years); 70% reduction in nonvertebral fractures
Reid, 2000[181]	Risedronate 2.5 or 5 mg/d + 1g/d Ca + 400 u/d vit D X 12 mos	Placebo + 1g/d Ca + 400 u/d vit D	290	≥7.5 mg prednisone	Ambulatory men and women, age 18-85, primarily RA, dermatologic, respiratory diseases	70% reduction in vertebral fractures
Wallach, 2000[183]	Risedronate 2.5 or 5 mg/d + 1000 mg/d Ca + 400 u/d vit D X 12 mos	Placebo + 1000 mg/d Ca + 400 u/d vit D	509	7.5 mg prednisone equivalent	184 Men/ 325 women (78% postmenopausal) , age range 18-85 years, primarily RA, PMR, TA, CILD, COPD, asthma, and others	2.5 mg risedronate: 58% reduction in vertebral fractures; 5 mg risedronate: 70% reduction in vertebral fractures

Key Question 3. What are the short- and long-term harms (adverse effects) of the therapies, and do these vary by any specific subpopulations?

Key Points

- Over a large body of evidence, no significant association was demonstrated between bisphosphonates and mild upper gastro-esophageal events including reflux and esophagitis.
- There is good evidence that etidronate is associated with a significant risk of serious upper GI events relative to placebo (OR for non-esophageal perforations ulcers and bleeds =1.32, CI 1.04 to 1.67; OR for serious esophageal events = 1.33, CI 1.05 to 1.68).
- Over a large body of evidence, no significant association has been demonstrated between bisphosphonates other than etidronate and serious upper gastrointestinal events.
- There is good evidence from RCTs that compared with placebo, raloxifene is associated with an increased risk of thromboembolic events (OR 2.11, 95% CI 1.51 to 3.01).
- There are no data from osteoporosis RCTs that describe the association between bisphosphonates or any other agents and the development of osteonecrosis. However, osteonecrosis of the jaws has been reported among cancer patients receiving intravenous bisphosphonates.[8]

Detailed Analysis

Below we describe the results that are statistically significant and/or clinically important. A large table displaying all of the adverse events analyses is attached as Appendix F. That appendix includes information on cancer, cardiac, dermatologic, gastrointestinal, gynecologic, immunologic, metabolic, musculoskeletal, neurological, psychiatric, and respiratory events.

All cause mortality: Among some 30 trials with a total of over 10,000 subjects, we found only one trial where there was a significant difference in odds ratio for deaths between arms. In a head-to-head trial of etidronate versus calcium (total N = 166), the editronate group had a lower odds ratio for death (0.36, 95% CI 0.13 to .92). However, in another trial that compared etidronate and placebo, the odds were 0.72 (95% CI 0.41 to 1.23).

Cardiac, Serious: Two studies specifically reported cardiac deaths. A placebo-controlled trial of alendronate showed no difference between groups. In one large observational study there was no difference in cardiac deaths between raloxifine and placebo.

Neurological - Cerebrovascular events: Cerebrovascular events were reported in two placebo-controlled trials of ibandronate, two observational studies of raloxefine, and one placebo-controlled trial of testosterone. No significant differences between any comparison groups were found regarding cerebrovascular events.

Hematologic - Thromboembolic events: We pooled nine placebo-controlled studies of raloxifine that reported thromboembolic events. Raloxefine subjects were significantly more likely to experience a thromboembolic event (OR 2.11, 95% CI 1.51 to 3.01) than placebo. One head-to-head trial of alendronate versus raloxefine showed no difference between the two drugs, as did one head-to-head trial of alendronate versus estrogen. One placebo-controlled trial of alendronate also showed no difference in arms. No other studies reported thromboembolic events.

Upper Gastrointestinal, mild – Reflux and esophageal: We pooled 25 placebo-controlled trials of alendronate which reported these events. Although more alendronate subjects reported these events, difference from placebo was not statistically significant (OR 1.02, 95% CI 0.94 to 1.11). We also found 15 placebo-controlled trials of risedronate which reported mild reflux and esophageal adverse events. Pooled results show that risedronate patients were less likely to report these events, but the difference was not statistically significant (OR 0.87, 95% CI 0.72 to 1.06).

We pooled two head-to-head trials of alendronate versus estrogen; alendronate patients had higher odds of having a mild reflux or esophageal event (OR 2.03, 95% CI 1.15 to 3.64).

One placebo-controlled trial of calcitonin reported events in this category; these events were reported only in the placebo group.

The following number and type of studies also reported mild reflux and esophageal events. When more than one study existed, we calculated a pooled odds ratio. All differences between comparison groups were insignificant regarding these adverse events.

Head-to-head
- 1 alendronate versus etidronate
- 1 alendronate versus risedronate
- 1 alendronate versus alendronate + PTH
- 1 alendronate versus calcitonin
- 1 alendronate versus PTH
- 1 alendronate versus raloxifine
- 2 alendronate versus Vitamin D

Placebo-controlled
- 2 ibandronate versus placebo
- 3 pamidronate versus placebo

Gastrointestinal, Serious (Esophageal, including esophageal ulcers): Eleven placebo-controlled studies of alendronate reported serious esophageal events, including ulcers. We pooled these trials; differences between alendronate and placebo were not significant. We also pooled eight placebo-controlled studies of risedronate; results were also insignificant. One placebo-controlled trial of etidronate reported serious esophageal events; etidronate subjects had significantly more of these events (OR 1.33, 95% CI 1.05 – 1.68). One placebo-controlled trial of ibandronate and one placebo-controlled trial of pamidronate reported no significant differences.

Gastrointestinal, Serious (Upper GI perforations, ulcers or bleeds, excluding esophageal): We found a) one head-to-head trial of alendronate versus pamidronate, b) one head-to-head trial of

alendronate versus risedronate, and c) two head-to-head trials of alendronate versus Vitamin D which reported adverse events in this category. None showed significant differences between comparison groups.

We found three placebo-controlled trials of etidronate which reported these events. We pooled the data and found that etidronate subjects had significantly more events (OR 1.32, 95% CI 1.04 to 1.67). There were two placebo-controlled studies of ibandronate reporting upper GI perforations, ulcers or bleeds (excluding esophageal). We pooled these studies; ibandronate subjects had significantly lower odds of these events than placebo (OR 0.33, 95% CI 0.14 to 0.76). Differences between placebo and pamidronate were insignificant when we pooled three trials which reported upper GI perforations, ulcers or bleeds (excluding esophageal). Likewise, differences between placebo and risedronate were insignificant when we pooled seven such trials.

Osteonecrosis: A systematic review on bisphosphonates and osteonecrosis of the jaws was published after we submitted our draft report.[8] The article focused on cancer patients. The authors concluded that the risk for osteonecrosis in patients taking bisphosphonates for low bone density is uncertain and warrants future research.

Summary and Discussion

- There is good evidence from RCTs that, compared with placebo, alendronate, ibandronate, risedronate, calcitonin, 1-34 PTH, and raloxifene prevent vertebral fractures.
- There is evidence from one RCT that, compared with placebo, 1-34 PTH prevents non-vertebral fractures.
- There is good evidence from RCTs that, compared with placebo, risedronate prevents both non-vertebral and hip fractures.
- There is good evidence from RCTs that, compared with placebo, alendronate prevents both non-vertebral and hip fractures.
- Based on limited data, within the bisphosphonate class, superiority for the prevention of fractures has not been demonstrated for any specific agent.
- Based on the Women's Health Initiative, but not on earlier meta-analyses, estrogen is associated with a reduced risk of hip fracture.
- Based on limited data, superiority for the prevention of vertebral fractures has not been demonstrated for bisphosphonates in comparison to calcitonin, calcium, or raloxifene. However, these studies were not designed or powered to detect fractures.
- Based on a large body of evidence, superiority for the prevention of fractures has not been demonstrated for bisphosphonates in comparison to estrogen.
- There are no data from RCTs on the effect of testosterone on the prevention of fractures.
- There are no data from RCTs on the effect of exercise relative to agents used to treat or prevent osteoporosis on fracture prevention.
- There is good evidence from RCTs that compared with placebo, raloxifene is associated with an increased risk of thromboembolic events (OR 2.11, 95% CI 1.51 to 3.01).
- Over a large body of evidence, no significant association was demonstrated between bisphosphonates and mild upper gastro-esophageal events including reflux and esophagitis.
- There is good evidence that etidronate is associated with a significant risk of serious upper GI events relative to placebo (OR for non-esophageal perforations ulcers and bleeds =1.32, CI 1.04 to 1.67; OR for serious esophageal events = 1.33, CI 1.05 to 1.68).
- Over a large body of evidence, no significant association has been demonstrated between bisphosphonates other than etidronate and serious upper gastrointestinal events.
- There are no data from osteoporosis RCTs that describe the association between bisphosphonates or any other agents and the development of osteonecrosis. However, osteonecrosis of the jaws has been reported among cancer patients receiving intravenous bisphosphonates.[8]

Table 40. Summary of Evidence:

Key Question	Level of Evidence	Conclusion
1. What are the comparative benefits in fracture reduction among and also within the following treatments for low bone-density:		
a. bisphosphonates	Good for most comparisons	Vertebral fractures: There is good evidence from RCTs that compared with placebo; the bisphosphonates alendronate, ibandronate and risedronate prevent vertebral fractures. Nonvertebral fractures: There is good evidence from RCTs that compared with placebo; alendronate and risedronate prevent both non-vertebral and hip fractures.
b. calcitonin	Fair to good	Calcitonin is effective relative to placebo in the prevention of fractures. No difference between calcitonin and bisphosphonates or estrogen have been demonstrated for the prevention of vertebral fractures.
c. calcium	Good	As a single agent, calcium is not effective in preventing fractures.
d. estrogen	Good	Estrogen is associated with a reduced risk of hip fracture.
e. PTH (teriparatide)	Good	Relative to placebo, teriparatide is effective in preventing vertebral and non-vertebral fractures.
f. SERMs (raloxefine)	Good	Relative to placebo, raloxefine is effective in preventing vertebral fractures.
g. testosterone	Poor	There are no data from RCTs to inform this question.
h. vitamin D	Good	Vitamin D is associated with a reduced risk of hip and nonvertebral fractures at doses of 700-800 IU/d.
i. exercise in comparison to above agents.	Poor	There are no data from RCTs to inform this question.

Table 40. Summary of Evidence (continued):

Key Question	Level of Evidence	Conclusion
2. How does fracture reduction resulting from treatments vary between individuals with different risks for fracture as determined by bone mineral density (borderline/low/severe), prior fractures (prevention vs. treatment), age, gender, glucocorticoid use, and other factors (e.g., community dwelling vs. institutionalized; vitamin D deficient vs. not)?	Poor Good Good	• There are no conclusive data about the benefit of using agents for osteoporosis for prevention relative to treatment. • Alendronate and risedronate reduce the risk of glucocorticoid-associated vertebral fractures. • There are essentially no data on the effect of agents to prevent or treat osteoporosis among specifically among men.
3. What are the short- and long-term harms (adverse effects) of the above therapies, and do these vary by any specific subpopulations?	Good	• There is no significant association between bisphosphonates and mild upper gastro-esophageal events including reflux and esophagitis. • Etidronate is associated with a significant risk of serious upper GI events relative to placebo. • No significant association has been demonstrated between bisphosphonates other than etidronate and serious upper gastrointestinal events. • There are no data from RCTs that describe the association between bisphosphonates or any other agents used to prevent or treat osteoporosis and the development of osteonecrosis. • Raloxifene is associated with an increased risk of thromboembolic events.

Future Research

Among therapies directed to prevent or treat osteoporosis, we did not find any studies that assessed the effect of testosterone in men on the development of fractures. Likewise, we did not find any studies with fracture outcomes that compared the effect of drugs with exercise.

More head-to-head trials powered to detect differences in fracture rates are needed.

Among subpopulations at risk for osteoporosis, there are limited and inconclusive data about the effect of agents to prevent or treat osteoporosis among men, transplant recipients and people who use corticosteroids regularly. There is little research data on people of color. Future research should address these areas.

Osteonecrosis among patients taking bisphosphonates for low bone density should be carefully monitored and reported in the scientific literature.

Reference List

1. Christiansen C. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94(6):646-50.

2. Lindsay R. Osteoporosis. A guide to Diagnosis, Prevention, and Treatment. New York: Raven Press; 1992.

3. Chrischilles EA, Butler CD, Davis CS, et al. A model of lifetime osteoporosis impact. Arch Intern Med 1991;151(10):2026-32.

4. US Congress OoTA. Hip Fracture Outcomes in People Age 50 and Over-Background Paper. Washington, DC: US Government Printing Office. 1994.

5. Kaufman JM, Johnell O, Abadie E, et al. Background for studies on the treatment of male osteoporosis: state of the art. Ann Rheum Dis 2000;59(10):765-72.

6. Jacobsen SJ, Goldberg J, Miles TP, et al. Race and sex differences in mortality following fracture of the hip. Am J Public Health 1992; 82(8):1147-50.

7. Ray NF, Chan JK, Thamer M, et al. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12(1):24-35.

8. Woo SB, Hellstein JW, Kalmar JR . Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144(10):753-61.

9. Muchmore DB. Raloxifene: A selective estrogen receptor modulator (SERM) with multiple target system effects. Oncologist 2000;5(5):388-92.

10. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet 1999;354(9193):1896-900.

11. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996 ;17(1):1-12.

12. Moher D, Pham B, Jones A, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352(9128):609-13.

13. Fullerton DS, Atherly DS. Formularies, therapeutics, and outcomes: new opportunities. Med Care 2004;42(4 Suppl):III39-44.

14. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328(7454):1490.

15. Yusuf S, Peto R, Lewis J, et al. Beta blockade during and after myocardial infarction: an overview of the randomized trials. Prog Cardiovasc Dis 1985;27(5):335-71.

16. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med 2006.

17. Hedges LV, Olkin I. Statistical Methods for Meta-Analysis. San Deigo, CA: Academic Press Inc; 1985.

18. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557-60.

19. Version 9.0. College Station, Texas: Stata Corp.; 2005.

20. StatXact 7 for Windows [computer program]. Version Version 7.0.1. Cambridge, MA: Cytel Software Corporation; 2005.

21. Cranney A, Wells G, Willan A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. Meta-analysis of alendronate for the treatment of postmenopausal women. Endocr Rev 2002;23(4):508-16.

22. Karpf DB, Shapiro DR, Seeman E, et al. Prevention of nonvertebral fractures by alendronate. A meta-analysis. Alendronate Osteoporosis Treatment Study Groups. JAMA 1997;277(14):1159-64.

23. Cranney A, Welch V, Adachi JD, et al. Etidronate for treating and preventing postmenopausal osteoporosis. Cochrane Database of Systematic Reviews 2005;(3)

24. Cranney A, Adachi JD, Homik JJEH, et al. Calcitonin for preventing and treating corticosteroid-induced osteoporosis. Cochrane Database of Systematic Reviews 2005;(3)

25. Papapoulos SE, Quandt SA, Liberman UA, et al. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. Osteoporos Int 2005;16(5):468-74.

26. Cranney A, Tugwell P, Adachi J, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23(4):517-23.

27. Cranney A, Tugwell P, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VI. Meta-analysis of calcitonin for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23(4):540-51.

28. Kanis JA, McCloskey EV. Effect of calcitonin on vertebral and other fractures. QJM 1999;92(3):143-9.

29. Stevenson M, Lloyd Jones M, De Nigris E, et al. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis. Health Technol Assess 2005;9(22):1-160.

30. Schachter HM, Clifford TJ, Cranney A, Barrowman NJ, Moher D. Raloxifene for primary and secondary prevention of osteoporotic fractures in postmenopausal women: a systematic review of efficacy and safety evidence. Ottawa, Canada: Canadian Coordinating Office for Health Technology Assessment. 2005.

31. Shea B, Wells G, Cranney A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. Endocr Rev 2002;23(4):552-9.

32. Nelson H, Nygren P, Freeman M, Benjamin K. Drug class review on estrogens. 2004.

33. Papadimitropoulos E, Wells G, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: Meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23(4):560-9.

34. Avenell A, Gillespie WJ, Gillespie LD, et al. Vitamin D and vitamin D analogues for preventing fractures associated with involutional and post-menopausal osteoporosis. Cochrane Database Syst Rev 2005;(3):CD000227.

35. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293(18):2257-64.

36. Reid IR, Brown JP, Burckhardt P, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. N Engl J Med 2002;346(9):653-61.

37. Chesnut III CH, Skag A, Christiansen C, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2004;19(8):1241-9.

38. Recker R, Stakkestad JA, Chesnut CH 3rd, et al. Insufficiently dosed intravenous ibandronate injections are associated with suboptimal antifracture efficacy in postmenopausal osteoporosis. Bone 2004 ;34(5):890-9.

39. Kim SH, Lim SK, Hahn JS. Effect of pamidronate on new vertebral fractures and bone mineral density in patients with malignant lymphoma receiving chemotherapy. The American journal of medicine 2004;116(8):524-8.

40. Grotz W, Nagel C, Poeschel D, et al. Effect of ibandronate on bone loss and renal function after kidney transplantation. Journal of the American Society of Nephrology : JASN 2001;12(7):1530-7.

41. Coco M, Glicklich D, Faugere MC, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. Journal of the American Society of Nephrology : JASN 2003;14(10):2669-76.

42. Ravn P, Clemmesen B, Riis BJ, et al. The effect on bone mass and bone markers of different doses of ibandronate: a new bisphosphonate for prevention and treatment of postmenopausal osteoporosis: a 1-year, randomized, double-blind, placebo-controlled dose-finding study. Bone 1996;19(5):527-33.

43. Ninkovic M, Love S, Tom BD, et al. Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. J Hepatol 2002;37(1):93-100.

44. Aris RM, Lester GE, Renner JB, et al. Efficacy of pamidronate for osteoporosis in patients with cystic fibrosis following lung transplantation. American journal of respiratory and critical care medicine 2000;162(3 Pt 1):941-6.

45. Reid IR, Wattie DJ, Evans MC, et al. Continuous therapy with pamidronate, a potent bisphosphonate, in postmenopausal osteoporosis. J Clin Endocrinol Metab 1994;79(6):1595-9.

46. Kananen K, Volin L, Laitinen K, et al. Prevention of bone loss after allogeneic stem cell transplantation by calcium, vitamin D, and sex hormone replacement with or without pamidronate. J Clin Endocrinol Metab 2005;90(7):3877-85.

47. Adami S, Passeri M, Ortolani S, et al. Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis. Bone 1995;17(4):383-90.

48. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348(9041):1535-41.

49. Bone HG, Downs RW Jr, Tucci JR, et al. Dose-response relationships for alendronate treatment in osteoporotic elderly women. Alendronate Elderly Osteoporosis Study Centers. J Clin Endocrinol Metab 1997;82(1):265-74.

50. Bonnick S, Rosen C, Mako B, et al. Alendronate vs calcium for treatment of osteoporosis in postmenopausal women. Bone 1998;23(Suppl 5):S476.

51. Chesnut CH, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. The American journal of medicine 1995;99(2):144-52.

52. Cummings SR, Black DM, Thompson DE, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. JAMA 1998;280(24):2077-82.

53. Dursun N, Dursun E, Yalcin S. Comparison of alendronate, calcitonin and calcium treatments in postmenopausal osteoporosis. Int J Clin Pract 2001;55(8):505-9.

54. Greenspan SL , Parker RA, Ferguson L, et al. Early changes in biochemical markers of bone turnover predict the long-term response to alendronate therapy in representative elderly women: a randomized clinical trial. J Bone Miner Res 1998;13(9):1431-8.

55. Hosking D, Chilvers CE, Christiansen C, et al. Prevention of bone loss with alendronate in postmenopausal women under 60 years of age. Early Postmenopausal Intervention Cohort Study Group. N Engl J Med 1998;338(8):485-92.

56. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. N Engl J Med 1995;333(22):1437-43.

57. McClung M, Clemmesen B, Daifotis A, et al. Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group. Annals of internal medicine 1998;128(4):253-61.

58. Pols HA, Felsenberg D, Hanley DA, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Foxamax International Trial Study Group. Osteoporos Int 1999;9(5):461-8.

59. Weinstein RS, Bone H, Tucci J, et al. Alendronate treatment of osteoporosis in elderly women. J Bone Miner Res 1994;9(Suppl 1):S144.

60. Herd RJ, Balena R, Blake GM, et al. The prevention of early postmenopausal bone loss by cyclical etidronate therapy: a 2-year, double-blind, placebo-controlled study. Am J Med 1997;103(2):92-9.

61. Iwamoto J TTIS. Effect of menatetrenone on bone mineral density and incidence of vertebral fractures in postmenopausal women with osteoporosis: a comparison with the effect of etidronate. Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association 2001;6(6):487-92.

62. Lyritis GP, Tsakalakos N, Paspati I, et al. The effect of a modified etidronate cyclical regimen on postmenopausal osteoporosis: a four-year study. Clin Rheumatol 1997;16(4):354-60.

63. Meunier PJ, Confavreux E, Tupinon I, et al. Prevention of early postmenopausal bone loss with cyclical etidronate therapy (a double-blind, placebo-controlled study and 1-year follow-up). J Clin Endocrinol Metab 1997;82(9):2784-91.

64. Montessori ML, Scheele WH, Netelenbos JC, et al. The use of etidronate and calcium versus calcium alone in the treatment of postmenopausal osteopenia: results of three years of treatment. Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA 1997;7(1):52-8.

65. Cantatore FP , Loperfido MC, Mancini L, et al. Effect of calcitonin or the anabolic steroid Decadurabolin on serum beta 2 microglobulin in osteoporotic postmenopausal women. J Rheumatol 1992;19(11):1753-5.

66. Stevenson JC, Abeyasekera G, Hillyard CJ, et al. Calcitonin and the calcium-regulating hormones in postmenopausal women: effect of oestrogens. Lancet 1981 ;1(8222):693-5.

67. Storm T, Thamsborg G, Steiniche T, et al. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322(18):1265-71.

68. Watts NB, Harris ST, Genant HK, et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis. N Engl J Med 1990; 323(2):73-9.

69. Wimalawansa SJ. A four-year randomized controlled trial of hormone replacement and bisphosphonate, alone or in combination, in women with postmenopausal osteoporosis. Am J Med 1998;104(3):219-26.

70. Jiang Y, Zhao JJ, Mitlak BH, et al. Recombinant human parathyroid hormone (1-34) teriparatide improves both cortical and cancellous bone structure. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research 2003;18(11):1932-41.

71. Clemmesen B, Ravn P, Zegels B, et al. A 2-year phase II study with 1-year of follow-up of risedronate (NE-58095) in postmenopausal osteoporosis. Osteoporos Int 1997;7(5):488-95.

72. Fogelman I, Ribot C, Smith R, et al. Risedronate reverses bone loss in postmenopausal women with low bone mass: results from a multinational, double-blind, placebo-controlled trial. BMD-MN Study Group. J Clin Endocrinol Metab 2000;85(5):1895-900.

73. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282(14):1344-52.

74. McClung M, Bensen W, Bolognese M, et al. Risedronate increases bone mineral density at the hip, spine and radius in postmenopausal women with low bone mass. Osteoporosis International 1998;8(Suppl 3):111.

75. McClung MR, Geusens P, Miller PD, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344(5):333-40.

76. Mortensen L, Charles P, Bekker PJ, et al. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. J Clin Endocrinol Metab 1998;83 (2):396-402.

77. Reginster J, Minne HW, Sorensen OH, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group . Osteoporos Int 2000;11(1):83-91.

78. Watts NB. Treatment of osteoporosis with bisphosphonates. Rheum Dis Clin North Am 1994;20(3):717-34.

79. Arnala I, Saastamoinen J, Alhava EM. Salmon calcitonin in the prevention of bone loss at perimenopause. Bone 1996;18(6):629-32.

80. Agrawal R, Wallach S, Cohn S, et al. Calcitonin treatment in osteoporosis. In: Calcitonin 1980. Proceedings of an international symposium held in Milan, October 1980. Excerpta Medica 1980;237-46.

81. Chesnut CH 3rd, Silverman S, Andriano K, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109(4):267-76.

82. Gennari C, Chierichetti SM, Bigazzi S, et al. Comparative effects on bone mineral content of calcium and calcium plus salmon calcitonin given in two different regimens in postmenopausal osteoporosis. Curr 1985;THER. RES., CLIN. EXP. 38(3):455-464.

83. Gruber HE, Ivey JL, Baylink DJ, et al. Long-term calcitonin therapy in postmenopausal osteoporosis. Metabolism 1984;33(4):295-303.

84. Healey JH, Paget SA, Williams-Russo P, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-treated temporal arteritis and polymyalgia rheumatica. Calcif Tissue Int 1996;58(2):73-80.

85. Hizmetli S, Elden H, Kaptanoglu E, et al. The effect of different doses of calcitonin on bone mineral density and fracture risk in postmenopausal osteoporosis. Int J Clin Pract 1998;52(7):453-5.

86. Overgaard K, Hansen MA, Jensen SB, et al. Effect of salcatonin given intranasally on bone mass and fracture rates in established osteoporosis: a dose-response study. BMJ 1992;305(6853):556-61.

87. Peyron R, Serrurier D, Edouard C, Ghozlan R, Mayoux-Benhamon A, Meunier PJ. Treatment of high remodelling vertebral osteoporosis with human calcitonin: a two year double-blind placebo-controlled trial in 93 patients. In: Christiansen C, Overgaard Ke. Osteoporosis. Copenhagen: Osteopress; 1990. p. 1430-3.

88. Rico H, Hernandez ER, Revilla M, et al. Salmon calcitonin reduces vertebral fracture rate in postmenopausal crush fracture syndrome. Bone Miner 1992;16(2):131-8.

89. Rico H, Revilla M, Hernandez ER, et al. Total and regional bone mineral content and fracture rate in postmenopausal osteoporosis treated with salmon calcitonin: a prospective study. Calcif Tissue Int 1995;56(3):181-5.

90. Ringe JD. [Treatment of primary osteoporosis with calcium and salmon calcitonin]. Deutsche medizinische Wochenschrift 1990;115(31-32): 1176-82.

91. Ringe JD, Welzel D. Salmon calcitonin in the therapy of corticoid-induced osteoporosis. European journal of clinical pharmacology 1987;33(1):35-9.

92. Sambrook P, Birmingham J, Kelly P. Prevention of corticosteroid-induced osteoporosis. NEJM 1993;328(24):1747-52.

93. Stock JL, Avioli LV, Baylink DJ. Calcitonin-salmon nasal spray reduces the incidence of new vertebral fractures in post-menopausal women: three-year interim results of the PROOF study. J Bone Miner Res 1997;12(suppl 1):S149.

94. Luengo M, Pons F, Martinez de Osaba MJ, et al. Prevention of further bone mass loss by nasal calcitonin in patients on long term glucocorticoid therapy for asthma: a two year follow up study. Thorax 1994;49(11):1099-102.

95. Prince RL, Devine A, Dhaliwal SS, et al. Effects of calcium supplementation on clinical fracture and bone structure: results of a 5-year, double-blind, placebo-controlled trial in elderly women. Arch Intern Med 2006;166(8):869-75.

96. Chevalley T, Rizzoli R, Nydegger V, et al. Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. Osteoporos Int 1994;4(5):245-52.

97. Hansson T, Roos B. The effect of fluoride and calcium on spinal bone mineral content: a controlled, prospective (3 years) study. Calcif Tissue Int 1987;40(6):315-7.

98. Recker RR, Hinders S, Davies KM, et al. Correcting calcium nutritional deficiency prevents spine fractures in elderly women. J Bone Miner Res 1996;11(12):1961-6.

99. Reid IR, Ames RW, Evans MC, et al. Effect of calcium supplementation on bone loss in postmenopausal women. N Engl J Med 1993;328(7):460-4.

100. Riggs BL, O'Fallon WM, Muhs J, et al. Long-term effects of calcium supplementation on serum parathyroid hormone level, bone turnover, and bone loss in elderly women. J Bone Miner Res 1998;13 (2):168-74.

101. Cauley JA, Robbins J, Chen Z, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003;290(13):1729-38.

102. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA 2002;288(3):321-33.

103. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. BMC Musculoskelet Disord 2001;2(1):7.

104. Wells G, Tugwell P, Shea B, et al. Meta-analyses of therapies for postmenopausal osteoporosis. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. Endocr Rev 2002;23(4):529-39.

105. Alexandersen P, Riis BJ, Christiansen C. Monofluorophosphate combined with hormone replacement therapy induces a synergistic effect on bone mass by dissociating bone formation and resorption in postmenopausal women: a randomized study. J Clin Endocrinol Metab 1999;84 (9):3013-20.

106. Bjarnason NH, Byrjalsen I, Hassager C, et al. Low doses of estradiol in combination with gestodene to prevent early postmenopausal bone loss. Am J Obstet Gynecol 2000;183(3):550-60.

107. Cauley JA, Black DM, Barrett-Connor E, et al. Effects of hormone replacement therapy on clinical fractures and height loss: The Heart and Estrogen/Progestin Replacement Study (HERS). Am J Med 2001;110(6):442-50.

108. Delmas PD, Confavreux E, Garnero P, et al. A combination of low doses of 17 beta-estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. Osteoporos Int 2000;11(2):177-87.

109. Eiken P, Nielsen SP, Kolthoff N. Effects on bone mass after eight years of hormonal replacement therapy. Br J Obstet Gynaecol 1997;104(6):702-7.

110. Gallagher JC, Fowler SE, Detter JR, et al. Combination treatment with estrogen and calcitriol in the prevention of age-related bone loss. J Clin Endocrinol Metab 2001;86(8):3618-28.

111. Genant HK, Lucas J, Weiss S, et al. Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. Estratab/Osteoporosis Study Group. Arch Intern Med 1997;157(22):2609-15.

112. Greenspan S, Bankhurst A, Bell N. Effects of alendronate and estrogen alone and in combination on bone mass and turnover in postmenopausal osteoporosis. J Bone Miner Res 1998;S174 (Abstract 1107).

113. Herrington DM, Reboussin DM, Brosnihan KB, et al. Effects of estrogen replacement on the progression of coronary-artery atherosclerosis. N Engl J Med 2000 ;343(8):522-9.

114. Hully S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postemenopausal women. JAMA 1998;280:605-13.

115. Ishida Y, Soh H, Tsuchida M, et al. Comarison of the effectiveness of hormone replacement therapy, bisphosphonate, calcitonin, vitamin D and vitamin K in postmenopausal . Bone 2001;28(Suppl 1):S224.

116. Komulainen M, Tuppurainen MT, Kroger H, et al. Vitamin D and HRT: no benefit additional to that of HRT alone in prevention of bone loss in early postmenopausal women. A 2.5-year randomized placebo-controlled study. Osteoporosis Int 1997;7:126-32.

117. Lees B, Stevenson JC. The prevention of osteoporosis using sequential low-dose hormone replacement therapy with estradiol-17 beta and dydrogesterone. Osteoporos Int 2001;12(4):251-8.

118. Lindsay R, Tohme JF. Estrogen treatment of patients with established postmenopausal osteoporosis. Obstet Gynecol 1990;76(2):290-5.

119. Lufkin EG, Wahner HW, O'Fallon WM, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. Ann Intern Med 1992;117(1):1-9.

120. Mosekilde L, Beck-Nielsen H, Sorensen OH, et al. Hormonal replacement therapy reduces forearm fracture incidence in recent postmenopausal women - results of the Danish Osteoporosis Prevention Study. Maturitas 2000;36(3):181-93.

121. Orr-Walker BJ, Evans MC, Clearwater JM, et al. Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women. Arch Intern Med 2000;160(14):2161-6.

122. Effects of hormone therapy on bone mineral density: results from the postmenopausal estrogen/progestin interventions (PEPI) trial. The Writing Group for the PEPI. JAMA 1996;276(17):1389-96.

123. Ravn P, Bidstrup M, Wasnich RD, et al. Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial. Annals of internal medicine 1999;131(12):935-42.

124. Recker RR, Davies KM, Dowd RM, et al. The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial. Ann Intern Med 1999; 130(11):897-904.

125. Weiss SR, Ellman H, Dolker M. A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Transdermal Estradiol Investigator Group. Obstet Gynecol 1999;94(3):330-6.

126. Cosman F, Nieves J, Woelfert L, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. J Bone Miner Res 2001;16(5):925-31.

127. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344(19):1434-41.

128. Ettinger B, Black DM, Mitlak BH, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282(7):637-45.

129. Lufkin EG, Whitaker MD, Nickelsen T, et al. Treatment of established postmenopausal osteoporosis with raloxifene: a randomized trial. J Bone Miner Res 1998;13(11):1747-54.

130. Nelson HD, Humphrey LL, Nygren P, et al. Postmenopausal hormone replacement therapy: scientific review. JAMA 2002;288(7):872-81.

131. Aloia JF, Vaswani A, Ellis K, et al. A model for involutional bone loss. J Lab Clin Med 1985;106(6):630-7.

132. Avenell A, Grant AM, McGee M, et al. The effects of an open design on trial participant recruitment, compliance and retention--a randomized controlled trial comparison with a blinded, placebo-controlled design. Clin Trials 2004;1(6):490-8.

133. Baeksgaard L, Andersen KP, Hyldstrup L. Calcium and vitamin D supplementation increases spinal BMD in healthy, postmenopausal women. Osteoporos Int 1998;8(3):255-60.

134. Caniggia A, Delling G, Nuti R, et al. Clinical, biochemical and histological results of a double-blind trial with 1,25-dihydroxyvitamin D3, estradiol and placebo in post-menopausal osteoporosis. Acta Vitaminol Enzymol 1984;6(2):117-28.

135. Chapuy MC, Arlot ME, Delmas PD, et al. Effect of calcium and cholecalciferol treatment for three years on hip fractures in elderly women. BMJ 1994;308(6936):1081-2.

136. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002;13(3):257-64.

137. Dawson-Hughes B, Harris SS, Krall EA, et al. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997;337(10):670-6.

138. Dukas L, Bischoff HA, Lindpaintner LS, et al. Alfacalcidol reduces the number of fallers in a community-dwelling elderly population with a minimum calcium intake of more than 500 mg daily. J Am Geriatr Soc 2004;52(2):230-6.

139. Gorai I, Chaki O, Taguchi Y, et al. Early postmenopausal bone loss is prevented by estrogen and partially by 1alpha-OH-vitamin D3: therapeutic effects of estrogen and/or 1alpha-OH-vitamin D3. Calcif Tissue Int 1999;65(1):16-22.

140. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365(9471):1621-8.

141. Geusens P, Dequeker J. Long-term effect of nandrolone decanoate, 1 alpha-hydroxyvitamin D3 or intermittent calcium infusion therapy on bone mineral content, bone remodeling and fracture rate in symptomatic osteoporosis: a double-blind controlled study. Bone Miner 1986;1(4):347-57.

142. Harwood RH, Sahota O, Gaynor K, et al. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. Age Ageing 2004;33(1):45-51.

143. Lips P, Graafmans WC, Ooms ME, et al. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med 1996;124(4):400-6.

144. Meyer HE, Smedshaug GB, Kvaavik E, et al. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res 2002;17(4):709-15.

145. Orimo H, Shiraki M, Hayashi T, et al. Reduced occurrence of vertebral crush fractures in senile osteoporosis treated with 1 alpha (OH)-vitamin D3 . Bone Miner 1987;3(1):47-52.

146. Orimo H, Shiraki M, Hayashi Y, et al. Effects of 1 alpha-hydroxyvitamin D3 on lumbar bone mineral density and vertebral fractures in patients with postmenopausal osteoporosis. Calcif Tissue Int 1994;54(5):370-6.

147. Ott SM, Chesnut CH 3rd. Calcitriol treatment is not effective in postmenopausal osteoporosis. Ann Intern Med 1989;110(4):267-74.

148. Peacock M, Liu G, Carey M, et al. Effect of calcium or 25OH vitamin D3 dietary supplementation on bone loss at the hip in men and women over the age of 60. J Clin Endocrinol Metab 2000;85(9):3011-9.

149. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000;15 (6):1113-8.

150. Sato Y, Maruoka H, Oizumi K. Amelioration of hemiplegia-associated osteopenia more than 4 years after stroke by 1 alpha-hydroxyvitamin D3 and calcium supplementation. Stroke 1997;28(4):736-9.

151. Sato Y, Manabe S, Kuno H, et al. Amelioration of osteopenia and hypovitaminosis D by 1alpha-hydroxyvitamin D3 in elderly patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1999;66(1):64-8.

152. Sato Y, Kuno H, Kaji M, et al . Effect of ipriflavone on bone in elderly hemiplegic stroke patients with hypovitaminosis D. Am J Phys Med Rehabil 1999;78(5):457-63.

153. Smith H, Anderson F, Raphael H, et al. Effect of annual intramuscular vitamin D supplementation on fracture risk: population-based, randomised, double-blind, placebo-controlled trial [abstract]. Osteoporosis International 2004;15(1):S8.

154. Tilyard MW, Spears GF, Thomson J, et al. Treatment of postmenopausal osteoporosis with calcitriol or calcium. N Engl J Med 1992;326(6):357-62.

155. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;326(7387):469.

156. Ushiroyama T, Ikeda A, Sakai M, et al. Effects of the combined use of calcitonin and 1 alpha-hydroxycholecalciferol on vertebral bone loss and bone turnover in women with postmenopausal osteopenia and osteoporosis: a prospective study of long-term and continuous administration with low dose calcitonin. Maturitas 2001;40(3):229-38.

157. Kushida K, Fukunaga M, Kishimoto H, et al. A comparison of incidences of vertebral fracture in Japanese patients with involutional osteoporosis treated with risedronate and etidronate: a randomized, double-masked trial. Journal of Bone and Mineral Metabolism 2004;22(5):469-78.

158. Fukunaga M, Kushida K, Kishimoto H, et al. A comparison of the effect of risedronate and etidronate on lumbar bone mineral density in Japanese patients with osteoporosis: a randomized controlled trial. Osteoporos Int 2002;13(12):971-9.

159. Guanabens N PARIALPFCLMAMdOMRMPPRJ. Alendronate is more effective than etidronate for increasing bone mass in osteopenic patients with primary biliary cirrhosis. The American journal of gastroenterology 2003;98(10):2268-74.

160. Iwamoto J, Takeda T, Ichimura S, et al. Comparative effects of treatment with etidronate and alendronate on bone resorption, back pain, and activities of daily living in elderly women with vertebral fractures. Keio J Med 2003;52(4):230-5.

161. Hosking D, Adami S, Felsenberg D, et al. Comparison of change in bone resorption and bone mineral density with once-weekly alendronate and daily risedronate: a randomised, placebo-controlled study. Current medical research and opinion 2003;19(5):383-94.

162. Rosen CJ, Hochberg MC, Bonnick SL, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. J Bone Miner Res 2005;20(1):141-51.

163. Muscoso E, Puglisi N, Mamazza C, et al. Antiresorption therapy and reduction in fracture susceptibility in the osteoporotic elderly patient: open study. Eur Rev Med Pharmacol Sci 2004;8(2):97-102.

164. Iwamoto J, Takeda T, Ichimura S, et al. Early response to alendronate after treatment with etidronate in postmenopausal women with osteoporosis. Keio J Med 2003;52(2):113-9.

165. Bone HG, Greenspan SL, McKeever C, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. Alendronate/Estrogen Study Group. J Clin Endocrinol Metab 2000;85 (2):720-6.

166. Harris ST, Eriksen EF, Davidson M, et al. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. J Clin Endocrinol Metab 2001;86(5):1890-7.

167. Lindsay R, Nieves J, Formica C, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. Lancet 1997;350(9077):550-5.

168. Body JJ, Gaich GA, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide. J Clin Endocrinol Metab 2002;87(10):4528-35.

169. Ishida Y, Kawai S. Comparative efficacy of hormone replacement therapy, etidronate, calcitonin, alfacalcidol, and vitamin K in postmenopausal women with osteoporosis: The Yamaguchi Osteoporosis Prevention Study. The American Journal of Medicine 2004;117(8):549-55.

170. Luckey M, Kagan R, Greenspan S, et al. Once-weekly alendronate 70 mg and raloxifene 60 mg daily in the treatment of postmenopausal osteoporosis. Menopause 2004;11(4):405-15.

171. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. JAMA 2003;289(19):2525-33.

172. Garcia-Delgado I PSG-FLRERJHF . Calcitonin, etidronate, and calcidiol treatment in bone loss after cardiac transplantation. Calcified tissue international 1997;60(2):155-9.

173. Lindsay R, Cosman F, Lobo RA, et al. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. The Journal of clinical endocrinology and metabolism 1999;84(9):3076-81.

174. Hodsman AB, Fraher LJ, Watson PH, et al. A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis. The Journal of clinical endocrinology and metabolism 1997;82(2):620-8.

175. Cosman F, Nieves J, Zion M, et al. Daily and cyclic parathyroid hormone in women receiving alendronate. N Engl J Med 2005;353(6):566-75.

176. Reid IR, Eastell R, Fogelman I, et al. A comparison of the effects of raloxifene and conjugated equine estrogen on bone and lipids in healthy postmenopausal women. Arch Intern Med 2004;164(8):871-9.

177. van Staa TP , Abenhaim L, Cooper C. Use of cyclical etidronate and prevention of non-vertebral fractures. Br J Rheumatol 1998;37(1):87-94.

178. Cohen S, Levy RM, Keller M, et al. Risedronate therapy prevents corticosteroid-induced bone loss: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum 1999;42(11):2309-18.

179. Voskaridou E, Terpos E, Spina G, et al. Pamidronate is an effective treatment for osteoporosis in patients with thalassemia major. 2003;

180. Blair MM, Carson DS, Barrington R. Bisphosphonates in the prevention and treatment of glucocorticoid-induced osteoporosis. J Fam Pract 2000;49(9):839-48.

181. Reid DM, Hughes RA, Laan RF, et al. Efficacy and safety of daily risedronate in the treatment of corticosteroid-induced osteoporosis in men and women: a randomized trial. European Corticosteroid-Induced Osteoporosis Treatment Study . J Bone Miner Res 2000;15(6):1006-13.

182. Adachi JD, Saag KG, Delmas PD, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. Arthritis Rheum 2001;44(1):202-11.

183. Wallach S, Cohen S, Reid DM, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. Calcif Tissue Int 2000;67(4):277-85.

184. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. N Engl J Med 1997;337(6):382-7.

185. Roux C, Oriente P, Laan R, et al. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. Ciblos Study Group. J Clin Endocrinol Metab 1998;83(4):1128-33.

186. Saag KG, Emkey R, Schnitzer TJ, et al. Alendronate for the prevention and treatment of glucocorticoid-induced osteoporosis. Glucocorticoid-Induced Osteoporosis Intervention Study Group. N Engl J Med 1998;339(5):292-9.

187. Jencen D, Reid D, Devogelaer JP, et al. Risedronate is safe and well tolerated in treating corticosteroid-induced osteoporosis. 2nd Meeting of the ASBMR-IBMS; San Francisco, CA. Marathon Multimedia.

188. Skingle SJ, Moore DJ, Crisp AJ. Cyclical etidronate increases lumbar spine bone density in patients on long-term glucocorticosteroid therapy. Int J Clin Pract 1997;51(6):364-7.

189. Jenkins EA, Walker-Bone KE, Wood A, et al. The prevention of corticosteroid-induced bone loss with intermittent cyclical etidronate. Scandinavian journal of rheumatology 1999;28(3):152-6.

190. Geusens P, Dequeker J, Vanhoof J, et al. Cyclical etidronate increases bone density in the spine and hip of postmenopausal women receiving long term corticosteroid treatment. A double blind, randomised placebo controlled study. Ann Rheum Dis 1998;57(12):724-7.

191. Cortet B, Hachulla E, Barton I, et al. Evaluation of the efficacy of etidronate therapy in preventing glucocorticoid-induced bone loss in patients with inflammatory rheumatic diseases. A randomized study. Rev Rhum Engl Ed 1999;66(4):214-9.

Abbreviations

Alendr	Alendronate
Calcit	Calcitonin
CI	confidence interval
Esoph	Esophagus
Estrog	Estrogen
Etidro	Etidronate
GI	Gastrointestinal
Ibandr	Ibandronate
Inj/app site rxns	Injection/ application site
iu	international units
IV	Intravenous
LFTs	Liver function tests
N/V	Nausea/vomiting
OR	Odds ratio
Pamidr	Pamidronate
PTH	Parathyroid hormone
Ralox	Raloxefine
RCT	randomized controlled trial
Rflx or esoph sx	Reflux or esophageal symptoms
Risedr	Risedonate
Tamox	Tamoxifen
Testos	Testosterone
UGI	Upper Gastrointestinal
Vit D	Vitamin D
Zoledr	Zolendronic Acid